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WO 01/13882 A1

(54) Title: METHODS OF LIGHTENING KERATINOUS TISSUE BY TOPICAL APPLICATION OF OXIME COMPOUND CONTAINING COMPOSITIONS

(57) Abstract: The present invention relates to methods of lightening keratinous tissue which comprise topically applying to the keratinous tissue in need of treatment a safe and effective amount of a composition comprising a safe and effective amount of an oxime compound and a dermatologically acceptable carrier for the oxime compound. More particularly, the present invention relates to methods of lightening skin, e.g., lightening hyperpigmented regions of skin, and of lightening skin by regulating melanin in skin, in the same manner as mentioned above.

METHODS OF LIGHTENING KERATINOUS TISSUE BY TOPICAL APPLICATION OF OXIME COMPOUND CONTAINING COMPOSITIONS

TECHNICAL FIELD

The subject invention relates to the field of lightening keratinous tissue, particularly mammalian keratinous tissue, by application of compositions to the keratinous tissue, e.g., skin. The invention further relates to methods of lightening keratinous tissue which involve the topical application of compositions containing oxime compounds. In particular, the present invention relates to methods of lightening hyperpigmented regions in skin by topical application of such compositions.

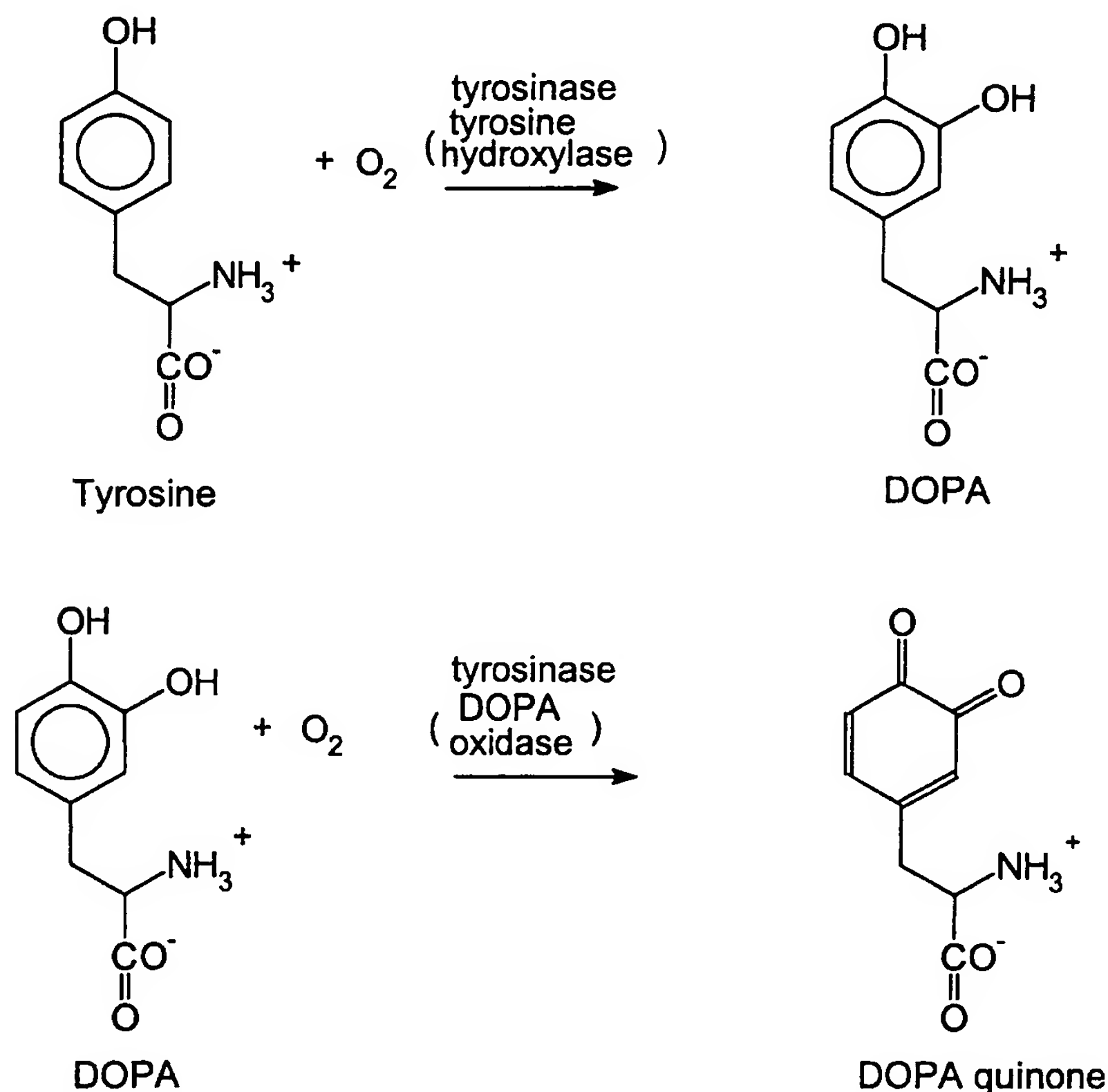
BACKGROUND OF THE INVENTION

Many personal care products currently available to consumers are directed primarily to improving the health and/or physical appearance of the various types of keratinous tissue which are present in mammals, particularly humans, e.g., the skin, hair, and nails. Among these products, many skin care products, in particular, are directed to delaying, minimizing or even eliminating histological changes typically associated with the aging of skin or environmental damage to skin, e.g., skin wrinkling.

Skin is subject to insults by many extrinsic and intrinsic factors. Extrinsic factors include ultraviolet radiation (e.g., from sun exposure), heat, wind, low humidity, harsh surfactants, abrasives, and the like. Intrinsic factors include chronological aging and other biochemical changes from within the skin. Whether extrinsic or intrinsic, these factors result in visible and/or tactile signs of skin aging, such as wrinkling, sagging, inelasticity, sallowness, changes in skin pigmentation and other histological changes associated with skin aging. To many people, such changes are a reminder of the disappearance of youth. As a result, treatments directed to the amelioration of such signs have become a booming business in youth-conscious societies. Treatments range from cosmetic creams and moisturizers to various forms of cosmetic surgery.

These extrinsic or intrinsic factors, e.g., chronic exposure to UV light and chronological aging, may result in regions of hyperpigmentation in the skin. Certain forms of non-uniform pigmentation or hyperpigmentation, e.g., age spots, freckles, pigment spots, brown spots, liver spots, melasma, cholasma, ephelides, senile lentigenes, suntan, melanoderma, hyperpigmented macules, sun spots, melanin spots, brown patches, pigment blotchiness, mottled pigmentation, inflammatory and post-inflammatory hyperpigmentation (e.g., from acne, abrasion, ingrown hairs, insect bites, etc.), pregnancy spots, moles, and the like involving concentration of melanin in the skin, are believed to result from changes in the melanocytes and the keratinocytes present in the epidermis. Melanocytes, which are located at the base of the epidermis, lose their normal regulation process with aging and/or exposure to extrinsic factors and produce excess pigment. This excess production leads to the formation of dense perinuclear clumps of melanin in keratinocytes within the epidermis, resulting in areas of hyperpigmentation.

Traditional therapy for hyperpigmented skin includes the application of certain skin lightening agents, such as kojic acid, arbutin, hydroquinone or ascorbic acid, which inhibit melanin formation. A mechanism of action for these materials which has been proposed in the art is tyrosinase inhibition and/or inhibition of other steps in melanin synthesis. Tyrosinase is present within the melanosomes in epidermal melanocytes and catalyzes the committed step in the formation of melanin from tyrosine. See Goldsmith, L. A., Physiology, Biochemistry, and Molecular Biology of the Skin, Oxford University Press, pp. 873-903 (N.Y. 1991). Tyrosinase catalyzes the hydroxylation of tyrosine and the oxidation of DOPA to DOPA quinone:



Binding of an inhibitor to the active site of tyrosinase results in decreased melanin formation. See generally Prota, G. Melanins and Melanogenesis, Academic Press, Inc., (San Diego 1992). The conversion of DOPA quinone to melanin occurs via non-enzymatic or spontaneous chemical reactions, some of which involve reactive oxygen or oxygen radicals.

Unfortunately, the efficacy of kojic acid and arbutin is marginal. Furthermore, hydroquinone has been associated with side effects due to cytotoxicity of the inhibitor's oxidized products. Ascorbic acid suffers from chemical stability problems and is therefore difficult to formulate into products having a shelf life needed for normal use.

Similarly, consumers often experience problems with other keratinous tissues like their hair or nails where lightening of such tissues is desirable in certain circumstances. For example, consumers often desire to lighten facial or other body hair or nail beds. There are, however, few products that are able to lighten such tissues in a safe and effective manner which is aesthetically pleasing to the consumer.

There is therefore a need for the development of keratinous tissue lightening methods which are more efficacious, safer, and which involve compositions which are easier to formulate.

It has now been found that topical compositions containing oxime compounds are useful for lightening keratinous tissue, including nails, hair, and skin (especially hyperpigmented regions of skin).

SUMMARY OF THE INVENTION

The present invention relates to methods of lightening keratinous tissue which comprise topically applying to the keratinous tissue in need of such treatment a safe and effective amount of a composition comprising a safe and effective amount of an oxime compound and a dermatologically acceptable carrier for the oxime compound. More particularly, the present invention relates to methods of lightening skin, e.g., lightening hyperpigmented regions of skin, and of lightening skin by regulating melanin in skin, in the same manner as mentioned above.

DETAILED DESCRIPTION OF THE INVENTION

It has been unexpectedly found that compositions which contain certain oxime compounds are useful for achieving lightening of keratinous tissue, including lightening of hyperpigmented regions in mammalian skin and lightening of hair and nail beds when applied topically to the respective keratinous tissue types. The subject invention is not limited to any particular mechanism of action, but is believed to operate by the inhibition of oxidative processes involved in the non-enzymatic steps in melanin production and/or by preventing reactive oxygen/oxygen radical stimulation (oxidative stress) of melanocytes which results in initiation of the melanin production pathway within the melanocytes, e.g., which can occur with UV or sunlight exposure or other intrinsic or extrinsic stress, such as that induced by inflammation, on the melanocyte.

All percentages and ratios used herein are by weight of the total composition and all measurements made are at 25°C, unless otherwise specified.

The compositions of the present invention can comprise, consist essentially of, or consist of, the essential as well as optional ingredients and components described herein. As used herein, "consisting essentially of" means that the composition or component may include additional ingredients, but only if the additional ingredients do not materially alter the basic and novel characteristics of the claimed compositions or methods.

All publications cited herein are hereby incorporated by reference in their entirety.

As used herein, "keratinous tissue" refers to keratin-containing layers disposed as the outermost protective covering of mammals which includes, but is not limited to, skin, hair, and nails (e.g., toenails, fingernails, hooves, cuticles, etc.).

The term "topical application", as used herein, means to apply or spread the compositions of the present invention onto the surface of the keratinous tissue. Preferred compositions of the present invention are those in a form intended to be left in contact with the keratinous tissue for an extended period (e.g., for several hours) after topical application, e.g., typical usage of a cream, lotion, moisturizer or the like.

The term "dermatologically-acceptable," as used herein, means that the compositions or components thereof so described are suitable for use in contact with mammalian keratinous tissue, e.g., that of humans, without undue toxicity, incompatibility, instability, allergic response, and the like.

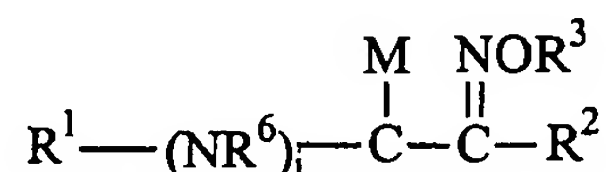
The term "safe and effective amount" as used herein means an amount of a compound or composition sufficient to significantly induce the intended benefit, but low enough to avoid serious side effects, i.e., to provide a reasonable benefit to risk ratio, within the scope of sound judgment of the skilled artisan.

The methods of the present invention are useful for lightening keratinous tissue, e.g., skin which is hyperpigmented. As used herein, "hyperpigmentation" means refers to concentrations of melanin in the skin which result in age spots, freckles, pigment spots, brown spots, liver spots, melasma, cholasma, ephelides, senile lentigenes, suntan, melanoderma, hyperpigmented macules, sun spots, melanin spots, brown patches, pigment blotchiness, mottled pigmentation, inflammatory and post-inflammatory hyperpigmentation (e.g., from acne, abrasion, ingrown hairs, insect bites, etc.), pregnancy spots, moles, and the like which are believed to result from changes in the melanocytes and the keratinocytes present in the epidermis.

The compositions of the present invention are especially useful for regulating keratinous tissue pigmentation associated with melanin. As used herein, regulating keratinous tissue pigmentation includes skin lightening. Skin lightening involves diminishing, minimizing and/or effacing existing melanin in skin (therapeutic), and/or delaying, minimizing and/or preventing the formation of melanin in skin (prophylactic), including hyperpigmented regions of skin.

Oxime Compound

The compositions of the present invention comprise a safe and effective amount of an oxime compound. The oxime compound may have the following structure:



wherein -R1 and -R2 are independently selected from the group consisting of alkyl, aryl, and heteroaryl, wherein R1 and R2 may be covalently bonded together to form a cyclic alkyl; -M is selected from the group consisting of =O, =S, --SR4 and -OR4 (when -M is -OR4 or -SR4, there is a hydrogen bonded to the carbon to which -M is bonded) and -R4 is selected from the group consisting of hydrogen, alkyl, aryl, and heteroaryl; -R3 is selected from the group consisting of hydrogen, alkyl, aryl and heteroaryl; and i is selected from the group consisting of one and zero.

When -R1 is aryl, it is preferably selected from substituted and unsubstituted, preferably unsubstituted, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyrrolyl, 3-pyrrolyl and phenyl; more preferably from 2-furyl, 2-thienyl, 2-pyrrolyl and phenyl; more preferably 2-furyl, and especially phenyl. Also preferred are these aryl substituted with lower alkyl or lower alkoxy, especially methyl or methoxy; preferred examples include 4-methylphenyl, 4-methoxyphenyl, 5-methylfuryl, and 3,5-dimethylfuryl.

When -R1 is alkyl, it is preferably selected from substituted and unsubstituted, preferably unsubstituted, C1-C18 alkyl, more preferably C1-C12, still more preferably C1-C8, more preferably still saturated, straight chain C1, C2, C3, C4, C5, C6, C7 or C8.

When -R2 is aryl, it is preferably selected from substituted and unsubstituted, preferably unsubstituted, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyrrolyl, 3-pyrrolyl and phenyl; more preferably from 2-furyl, 2-thienyl, 2-pyrrolyl and phenyl; more preferably 2-furyl, and especially phenyl. Also preferred are these aryl substituted with lower alkyl or lower alkoxy, especially methyl or methoxy; preferred examples include 4-methylphenyl, 4-methoxyphenyl, 5-methylfuryl, and 3,5-dimethylfuryl.

When -R2 is alkyl, it is preferably selected from substituted and unsubstituted, preferably unsubstituted, C1-C18 alkyl, more preferably C1-C12, still more preferably C1-C8, more preferably still saturated, straight chain C1, C2, C3, C4, C5, C6, C7 or C8.

When -R4 is aryl, it is preferably a substituted or unsubstituted, preferably unsubstituted phenyl. When -R4 is alkyl, it is preferably selected from substituted and unsubstituted, preferably unsubstituted, C1-C18, more preferably C1-C6, more preferably C1-C2, more preferably C1. -R4 is more preferably hydrogen.

When -R3 is aryl, it is preferably a substituted or unsubstituted, preferably unsubstituted, phenyl. When -R3 is alkyl, it is preferably selected from substituted and unsubstituted, preferably unsubstituted, C1-C18 alkyl, more preferably C1-C12, even more preferably C1-C6, still more preferably C1-C8, and even still more preferably C1. Most preferably, however, -R3 is hydrogen.

When -R6 is aryl, it is preferably a substituted or unsubstituted, preferably unsubstituted, phenyl. When -R6 is alkyl, it is preferably a substituted or unsubstituted, preferably unsubstituted, C1-C18 alkyl, more preferably C1-C12, more preferably C1-C6, more preferably C1-C8, more preferably C1. -R6 is more preferably hydrogen.

Preferred oxime compounds for use in the present invention include syn- and anti-forms or mixtures thereof. As used herein relative to monoxime-type compounds, "anti" and "syn" refer to the positioning of the -OR3 group with respect to the -M group. In the anti position, -OR3 is proximate to -M; in the syn position, -OR3 is distal to -M. Approximately equal amounts of the syn- and anti- forms of the same compound are preferred mixtures.

Preferred compounds for use in the present invention which conform to the above structural formula include di-(2-furyl) ethanedione syn-monooxime, di-(2-furyl)ethanedione anti-monooxime, di-(5-methyl-2-furyl) ethanedione syn-monooxime, di-(5-ethyl-2-furyl) ethanedione syn-monooxime, di-(4-ethyl-2-furyl) ethanedione syn-monooxime, di-(4-ethyl-2-furyl) ethanedione anti-monooxime, and di-(5-ethyl-2-

furyl) ethanedione anti-monooxime; more preferred are di-(2-furyl) ethanedione syn-monooxime, di-(2-furyl) ethanedione anti-monooxime, di-(5-methyl-2-furyl) ethanedione syn- or anti-monooxime, di-(5-ethyl-2-furyl) ethanedione syn- or anti-monooxime and di-(4-ethyl-2-furyl) ethanedione syn- or anti-monooxime; more preferred are di-(2-furyl) ethanedione syn- or anti-monooxime, di-(2-furyl) ethanedione anti-monooxime and di-(5-methyl-2-furyl) ethanedione syn- or anti-monooxime, still more preferred is di-(2-furyl) ethanedione syn- or anti-monooxime.

Compounds which are also useful in the present invention include syn or anti di-(2-furyl)-2-mercapto ethaneone oxime, syn or anti di-(2-furyl)-2-methylmercapto ethaneone oxime, syn or anti di-(2-furyl) thioethaneone monooxime; more preferred are syn or anti di-(2-furyl)-2-mercapto ethaneone oxime, and syn or anti di-(2-furyl)-2-methylmercapto ethaneone oxime; more preferred is syn or anti di-(2-furyl)-2-mercapto ethaneone oxime.

Compounds which are also useful in the present invention include 1-methyl-2-phenyl ethanedione syn-monooxime, 1-methyl-2-phenyl ethanedione anti-monooxime, 1-ethyl-2-phenyl ethanedione syn-monooxime, 1-ethyl-2-phenyl ethanedione anti-monooxime, 1-n-propyl-2-phenyl ethanedione syn- or anti-monooxime, 1-n-hexyl-2-phenyl ethanedione syn- or anti-monooxime, 1-methyl-2-(4-methoxyphenyl) ethanedione syn- or anti-monooxime, 1-methyl-2-(4-methylphenyl) ethanedione syn- or anti-monooxime, 1-(2-furyl) 2-phenyl ethanedione syn- or anti-monooxime, 1-(2-thienyl) 2-phenyl ethanedione syn- or anti-monooxime, 1-(2-pyrrolyl)-2-phenyl ethanedione syn-monooxime, 1-(2-pyrrolyl)-2-phenyl ethanedione anti-monooxime, 1-(N-methyl-2-pyrrolyl)-2-phenyl ethanedione syn-monooxime, 1-(N-methyl-2-pyrrolyl)-2-phenyl ethanedione anti-monooxime, and 1,2-dimethyl ethanedione syn- or anti-monooxime; more preferably 1-methyl-2-phenyl ethanedione syn-monooxime, 1-methyl-2-phenyl ethanedione anti-monooxime, 1-ethyl-2-phenyl ethanedione syn-monooxime, 1-ethyl-2-phenyl ethanedione anti-monooxime, 1-n-propyl-2-phenyl ethanedione syn- or anti-monooxime, 1-n-hexyl-2-phenyl ethanedione syn- or anti-monooxime, 1-methyl-2-(4-methoxyphenyl) ethanedione syn- or anti-monooxime, 1-methyl-2-(4-methylphenyl) ethanedione syn- or anti-monooxime, 1-(2-furyl) 2-phenyl ethanedione syn-monooxime and 1-(2-thienyl) 2-phenyl ethanedione syn-monooxime; more preferred are 1-methyl-2-phenyl ethanedione syn-monooxime, 1-methyl-2-phenyl ethanedione anti-monooxime and 1-ethyl-2-phenyl ethanedione syn-monooxime; still more preferred is 1-n-hexyl-2-phenyl ethanedione syn-monooxime.

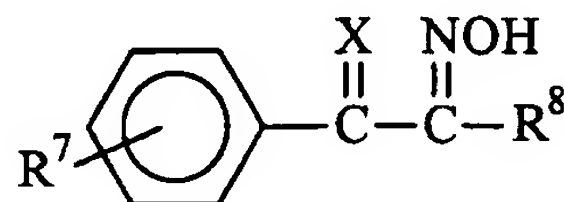
Compounds which are also useful in the present invention include N-phenyl-2-oxopropanamide oxime, N-phenylmethyl-2-oxopropanamide oxime, N-(2-furyl-5-methyl)-2-oxopropanamide oxime, and N-(2-furyl)-2-oxopropanamide oxime; more preferred are N-phenyl-2-oxopropanamide oxime, N-phenylmethyl-2-oxopropanamide oxime and N-(2-furyl-5-methyl)-2-oxopropanamide oxime; still more preferred is N-phenyl-2-oxopropanamide oxime.

Additional oxime compounds which are useful in the present invention include 1H-indole-2,3-dione-3-oxime, 1-methyl-indole-2,3-dione-3-oxime, 1-ethyl-indole-2,3-dione-3-oxime, 1-propyl-indole-2,3-dione-3-oxime, 1-phenyl-indole-2,3-dione-3-oxime, and 1-(4-ethylphenyl)-indole-2,3-dione-3-oxime; more

preferred is 1H-indole-2,3-dione-3-oxime, 1-methyl-indole-2,3-dione-3-oxime and 1-ethyl-indole-2,3-dione-3-oxime; more preferred is 1H-indole-2,3-dione-3-oxime.

For oxime compounds useful in the present invention named above, the lack of a designation of syn- or anti- is nonspecific and means either form alone or a mixture of the two.

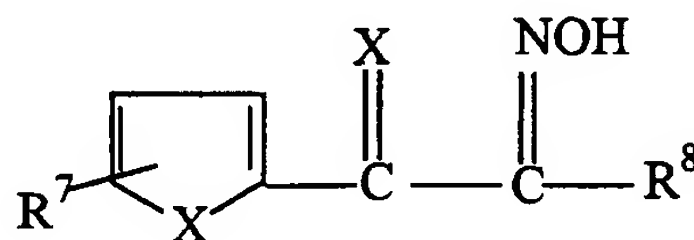
Another preferred oxime compound useful in the present invention has the following structural formula:



wherein =X is =O or =S, -R7 is hydrogen or from 0 to 5 alkyl substituents, and -R8 is C1-C8 alkyl. Preferably, =S is =O. Preferably, -R7 are hydrogen or lower alkyls, more preferably C1-C3, especially methyl. Preferably -R7 are saturated when it is alkyl. Furthermore, preferably -R7 are unsubstituted and straight chain when it is alkyl. Preferred -R7 is hydrogen or a mono-substituent, preferably in the 4-position.

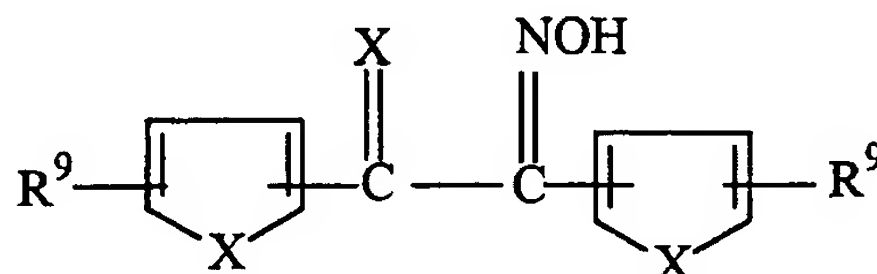
Preferred -R8 is saturated. Preferred -R8 is unsubstituted. Preferred -R8 is C1-C3, especially C1. Preferably, the oxime compound is 1-phenyl-1,2-propanedione-2-oxime.

In another embodiment of the present invention, the oxime compound may have the following structural formula:



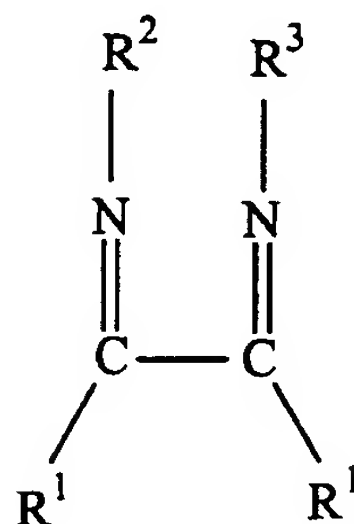
wherein each X is independently O or S, -R7 is from 1 to 3 alkyl substituents, and -R8 is C4-C8 alkyl. Preferred X is O. Preferred -R7 are in the 3-position and/or 5-position. Preferred -R7 is a mono-substituent in the 5-position; otherwise preferred -R7 and -R8 are as provided above.

In another embodiment, the oxime compound useful in the present invention has the following structure:



wherein each X is independently O or S, no more than one -R9 is hydrogen, and one or both -R9 are independently from 1 to 3 alkyl substituents. Preferred X is O. Preferred -R9 are lower alkyl, preferably C1-C3, especially methyl. Preferred -R9 are saturated. Preferred -R9 are unsubstituted. Preferred -R9 are straight chain. Preferred -R9 are in the 3-position and/or the 5-position. Preferred -R9 are mono-substituents in the 5-position.

The oxime compound of the present invention may also have the following α -diamine compound structural formula:



wherein each --R1 is independently selected from the group consisting of alkyl, aryl, heteroaryl and heterocyclic, or the --R1's are covalently bonded together to form a cyclic alkyl or heterocyclic ring; --R2 and --R3 are --OR4, in which case there is no bond or a polar bond between --R2 and the nitrogen covalently bonded to --R3, each --R4 being independently selected from the group consisting of hydrogen, alkyl and aryl except that both --R4 's are not methyl when both --R1 's are furyl; or --R2 is --O-- and is covalently bonded to the nitrogen which is covalently bonded to --R3, and --R3 is --O-- (there being a + charge on the nitrogen to which it is bonded) or nil.

In another embodiment the oxime compound consists essentially of compounds wherein =NR2 and =NR3 are in amphi configuration when both --R2 and --R3 are --OH, and when both --R1 's are furyl or the --R1 's are covalently bonded together to form a cyclohexanedione structure.

In any case the following measures are preferred. Preferably both --R1 's are the same moiety. Preferably both --R4 's are the same moiety.

When --R1 is aryl, --R1 is preferably selected from substituted and unsubstituted, preferably unsubstituted, 2-hydroxyphenyl and phenyl.

When --R1 is heteroaryl, --R1 is preferably selected from substituted and unsubstituted, preferably unsubstituted, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyrrolyl, 2-imadazolyl, 1-pyrazolyl, 2-pyrazinyl, 2-pyrimidinyl, 3-pyridazinyl, 3-isoquinolyl, 8-purinyl, 1-phthalazinyl, 2-quinoxaliny, 3-furazanyl, 3-isoxazolyl, 2-tetrazolyl and 5-tetrazolyl; more preferably from 2-furyl, 3-furyl, 2-thienyl, 3-thienyl and 2-pyrrolyl; more preferably still from 2-furyl and 3-furyl. Most preferably --R1 is 2-furyl.

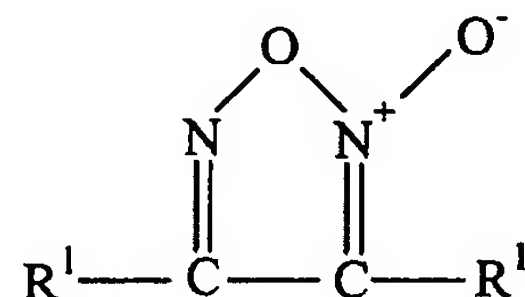
When --R1 is heterocyclic, --R1 is preferably the saturated analog of the preferred heteroaryls specified in the previous paragraph; most preferred is 2-tetrahydrofuryl.

When --R1 is alkyl, --R1 is preferably selected from substituted and unsubstituted, preferably unsubstituted, C1-C20 alkyl, more preferably C1-C18, more preferably C1-C12, more preferably still C1-C6, more preferably C1-C2, most preferably C1. Preferred alkyl --R1 's are alkanyls. Preferred alkanyls are straight chain.

When --R1 is substituted, each substituent is preferably selected from alkyl and aryl. When the substituent is an alkyl, it is preferably selected from C1-C20 alkyl, more preferably C1-C18, more

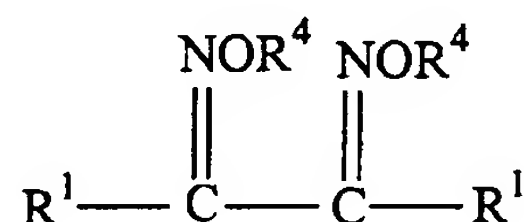
preferably C1-C12, more preferably still C1-C6, more preferably C1-C2, most preferably C1. When the substituent is an aryl, it is preferably phenyl.

Preferred oxime compounds which are useful in the present invention include those having the following α -diamine structural formula:



wherein --R1 is as defined hereinabove.

Preferred oxime compounds useful in the present invention include those having the following α -diamine structural formula:



wherein --R1 and --R4 are as defined hereinabove. In certain embodiments, such compounds are in the amphi configuration.

Most preferably --R4 is hydrogen.

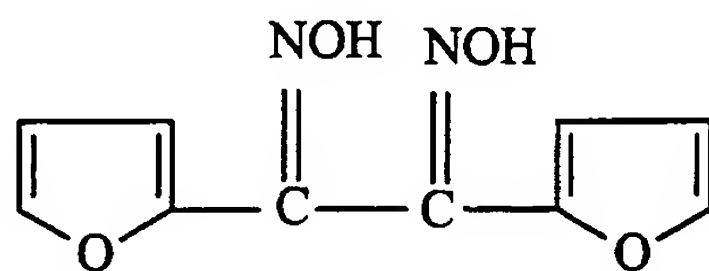
When --R4 is aryl, it is unsubstituted or substituted, preferably unsubstituted; preferably --R4 is phenyl.

When --R4 is a substituted aryl, the substituent is preferably --OH. When --R4 is alkyl, it is unsubstituted or substituted, preferably unsubstituted, preferably selected from C1 -C20, more preferably C2-C18, more preferably C2-C12, more preferably C2-C6, more preferably still C2-C4, most preferably C2. When --R4 is a substituted alkyl, preferred substituents are selected from --OH, =O, carboxy, --NH2, --NHR7 and --NR72, wherein --R7 is alkyl or aryl.

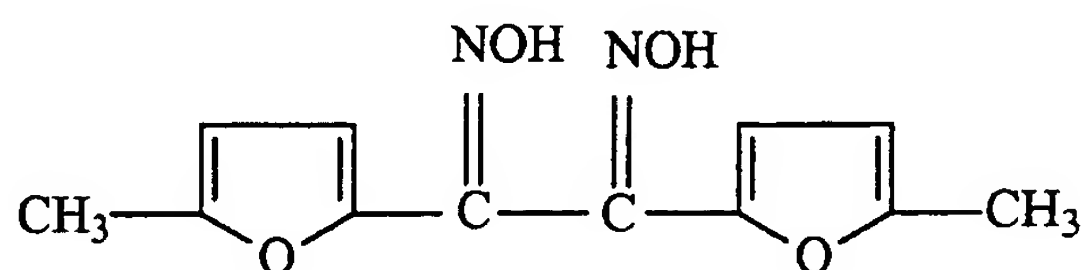
Preferred oxime compounds useful in the present invention include di-(2-furyl) ethanedione amphi-dioxime, di-(5-methyl-2-furyl) ethanedione amphi-dioxime, di-(4-methyl-2-furyl) ethanedione amphi-dioxime, di-(5-ethyl-2-furyl) ethanedione amphi-dioxime, di-(4-ethyl-2-furyl) ethanedione amphi-dioxime, di-(5-propyl-2-furyl) ethanedione amphi-dioxime, and di-(4-propyl-2-furyl) ethanedione amphi-dioxime; more preferred are di-(2-furyl) ethane-dione amphi-dioxime, di-(5-methyl-2-furyl) ethanedione amphi-dioxime, di-(4-methyl-2-furyl) ethanedione amphi-dioxime, di-(5-ethyl-2-furyl) ethanedione amphi-dioxime, and di-(4-ethyl-2-furyl) ethanedione amphi-dioxime; still more preferred is di-(2-furyl) ethanedione amphi-dioxime which is also referred to as 2-furildioxime. While the amphi form is preferred, mixtures of it with other forms (anti and/or syn) can be utilized, especially mixtures with approximately equal content of amphi and anti forms. As used herein, "amphi", "amphi form", and "amphi position" refer to the positioning of the --R2 and --R3 groups of the α -diamine oxime compounds relative to one another

such that the --R2 and --R3 groups point in the same direction as opposed to anti or syn forms wherein the --R2 and --R3 groups point in opposite directions away from or toward each other, respectively.

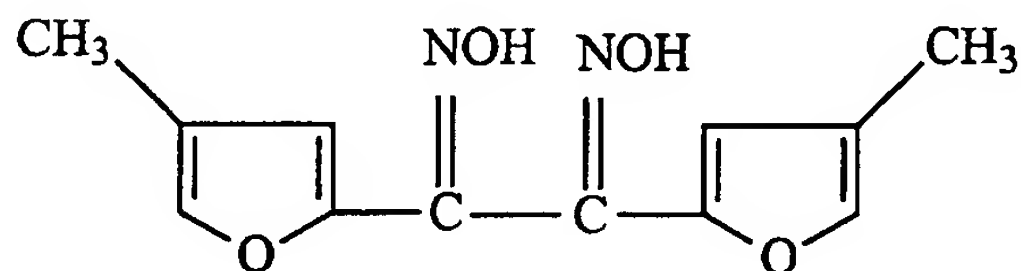
Representative structures include:



di-(2-furyl) ethanedione amphi-dioxime,

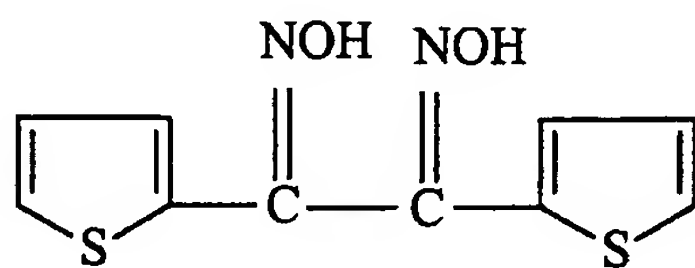


di-(5-methyl-2-furyl) ethanedione amphi-dioxime, and

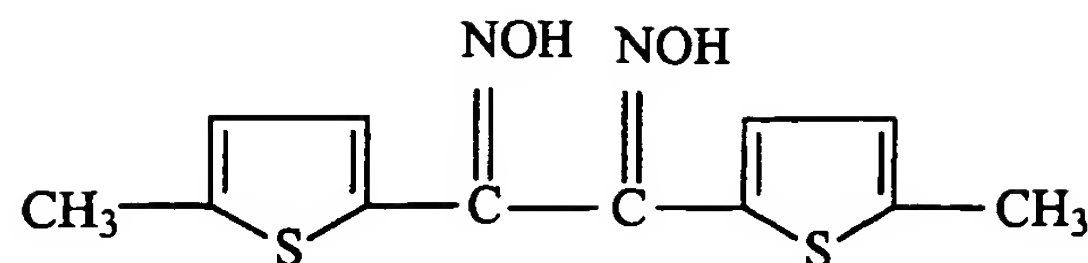


di-(4-methyl-2-furyl) ethanedione amphi-dioxime.

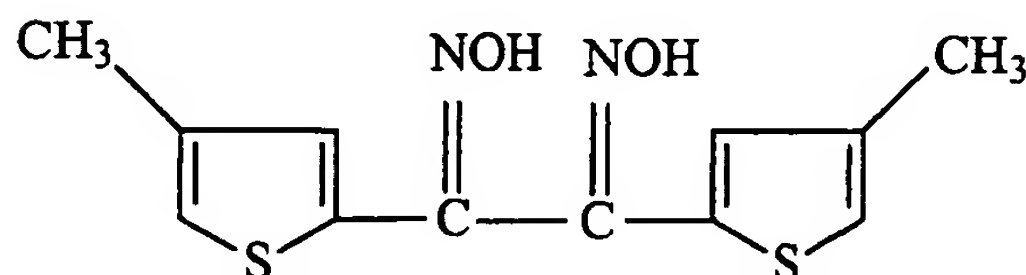
Compounds also preferred for use in the present invention include di-(2-thienyl) ethanedione amphi-dioxime, di-(5-methyl-2-thienyl) ethanedione amphi-dioxime, di-(4-methyl-2-thienyl) ethanedione amphi-dioxime, di-(5-ethyl-2-thienyl) ethanedione amphi-dioxime, and di-(5-propyl-2-thienyl) ethanedione amphi-dioxime; more preferred are di-(2-thienyl) ethanedione amphi-dioxime, di-(5-methyl-2-thienyl) ethanedione amphi-dioxime, and di-(4-methyl-2-thienyl) ethanedione amphi-dioxime; still more preferred is di-(2-thienyl) ethanedione amphi-dioxime. While the amphi form is preferred, mixtures of it with other forms (anti and/or syn) can be utilized, especially mixtures with approximately equal content of amphi and anti forms. Representative structures include:



di-(2-thienyl) ethanedione amphi-dioxime,

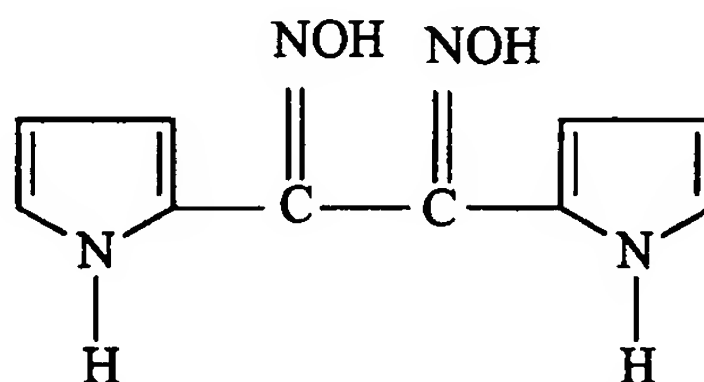


di-(5-methyl-2-thienyl) ethanedione amphi-dioxime,

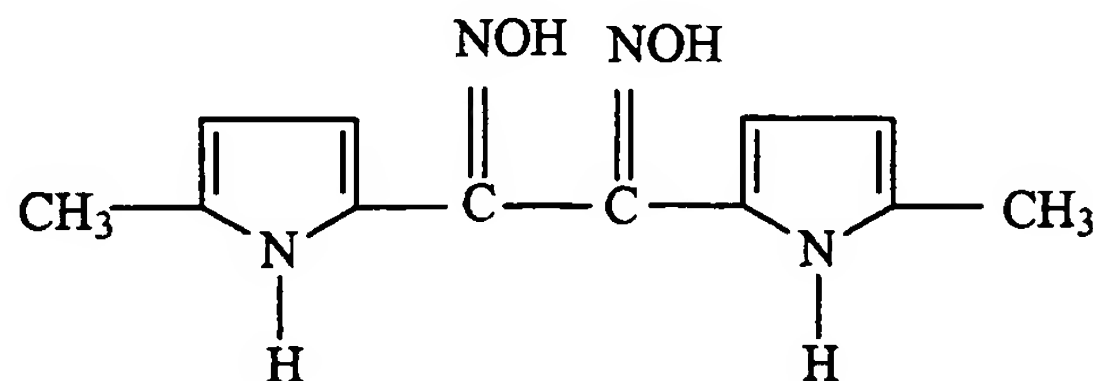


di-(4-methyl-2-thienyl) ethanedione amphi-dioxime.

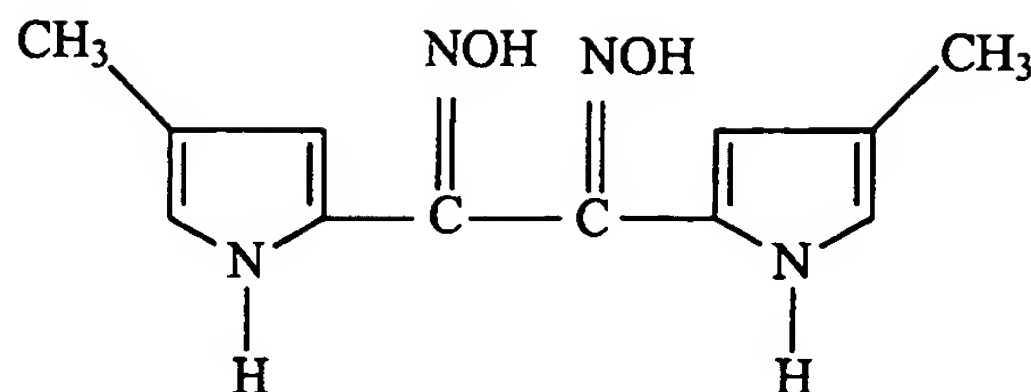
Compounds also preferred for use in the present invention include di-(2-pyrrolyl) ethanedione amphi-dioxime, di-(5-methyl-2-pyrrolyl) ethanedione amphi-dioxime, di-(4-methyl-2-pyrrolyl) ethanedione amphi-dioxime, di-(5-ethyl-2-pyrrolyl) ethanedione amphi-dioxime, di-(4-ethyl-2-pyrrolyl) ethanedione amphi-dioxime, di-(5-propyl-2-pyrrolyl) ethanedione amphi-dioxime, and di-(5-propyl-2-pyrrolyl) ethanedione amphi-dioxime; more preferred are di-(2-pyrrolyl) ethanedione amphi-dioxime, di-(5-methyl-2-pyrrolyl) ethanedione amphi-dioxime, di-(4-methyl-2-pyrrolyl) ethanedione amphi-dioxime, di-(5-ethyl-2-pyrrolyl) ethanedione amphi-dioxime, and di-(4-ethyl-2-pyrrolyl) ethanedione amphi-dioxime; still more preferred are di-(2-pyrrolyl) ethanedione amphi-dioxime, di-(5-methyl-2-pyrrolyl) ethanedione amphi-dioxime, and di-(4-methyl-2-pyrrolyl) ethanedione amphi-dioxime; more preferred still is di-(2-pyrrolyl) ethanedione amphi-dioxime. While the amphi form is preferred, mixtures of it with other forms (anti and/or syn) can be utilized, especially mixtures with approximately equal content of amphi and anti forms. Representative structures include:



di-(2-pyrrolyl) ethanedione amphi-dioxime,

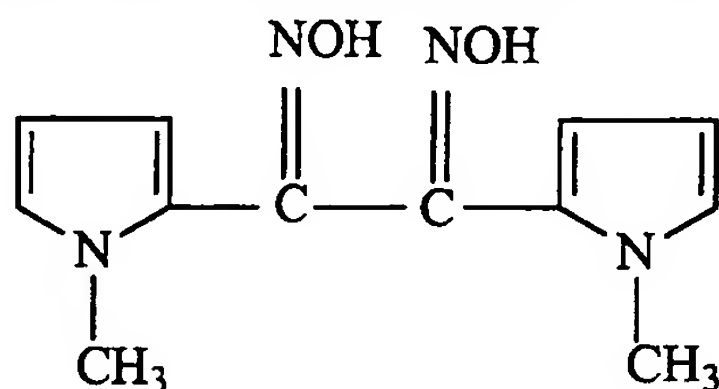


di-(5-methyl-2-pyrrolyl) ethanedione amphi-dioxime, and

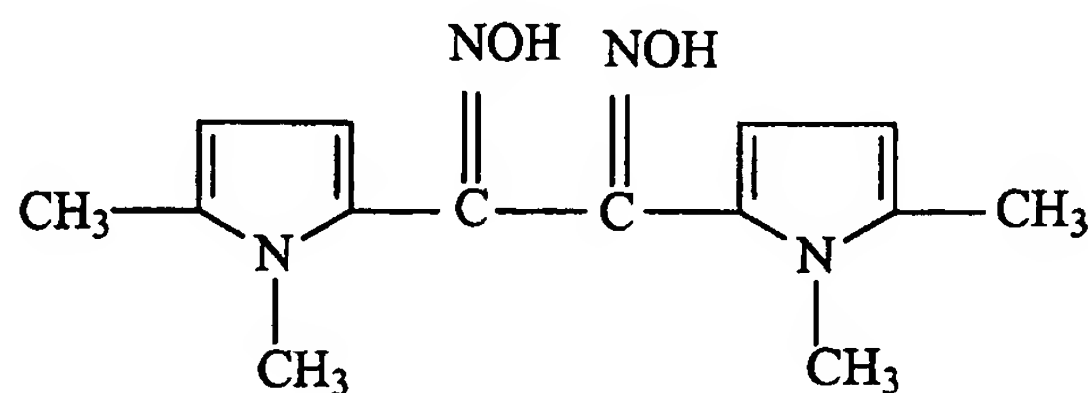


di-(4-methyl-2-pyrrolyl) ethanedione amphi-dioxime.

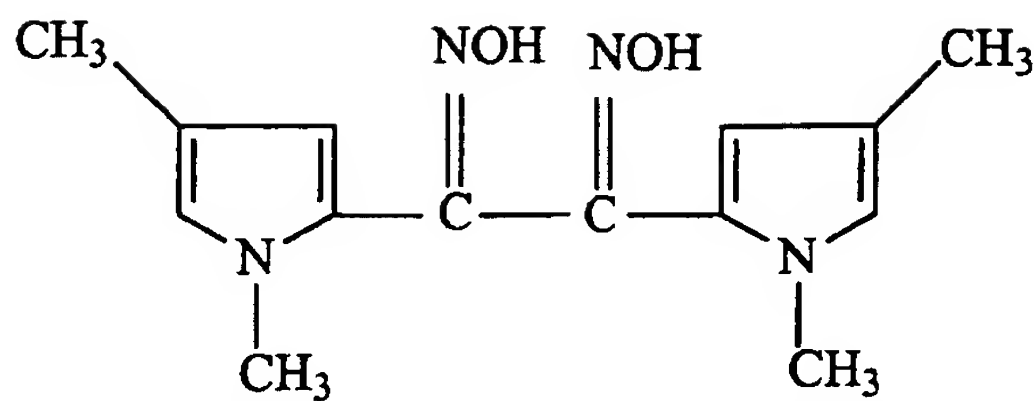
Compounds also preferred for use in the present invention include di-(1-methyl-2-pyrrolyl) ethanedione amphi-dioxime, di-(1,5-dimethyl-2-pyrrolyl) ethanedione amphi-dioxime, di-(1-methyl-5-ethyl-2-pyrrolyl) ethanedione amphi-dioxime, di-(1-methyl-5-propyl-2-pyrrolyl) ethanedione amphi-dioxime, and di-(1-methyl-2-pyrrolyl) ethanedione amphi-dioxime; more preferred are di-(1-methyl-2-pyrrolyl) ethanedione amphi-dioxime, di-(1,5-dimethyl-2-pyrrolyl) ethanedione amphi-dioxime, di-(1-methyl-dimethyl-2-pyrrolyl) ethanedione amphi-dioxime, di-(1-methyl-5-propyl-2-pyrrolyl) ethanedione amphi-dioxime; still more preferred is di-(1-methyl-2-pyrrolyl) ethanedione amphi-dioxime. While the amphi form is preferred, mixtures of it with other forms (anti and/or syn) can be utilized, especially mixtures with approximately equal content of amphi and anti forms. Representative structures include:



di-(1-methyl-2-pyrrolyl) ethanedione amphi-dioxime,

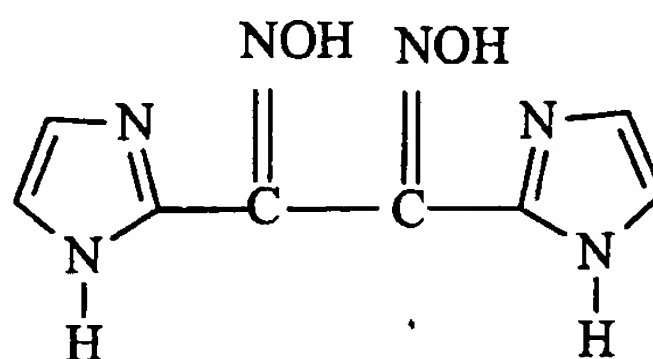


di-(1,5-dimethyl-2-pyrrolyl) ethanedione amphi-dioxime, and

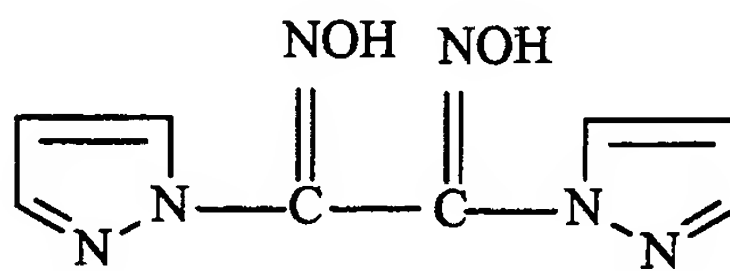


di-(1,4-methyl-2-pyrrolyl) ethanedione amphi-dioxime.

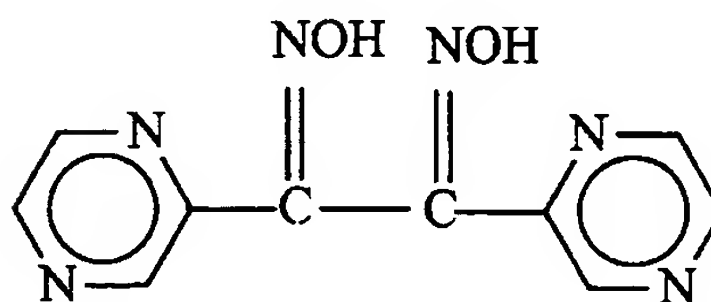
Compounds also preferred for use in the present invention include:



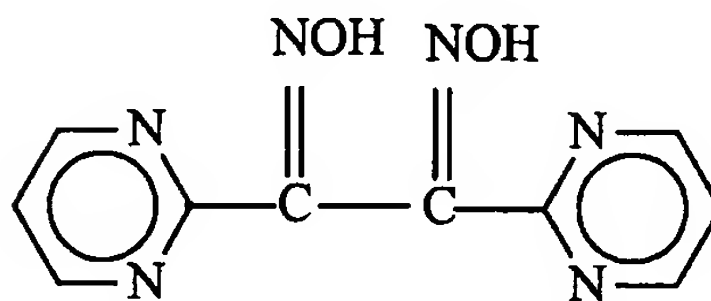
di-(2-imadazolyl) ethanedione amphi-dioxime,



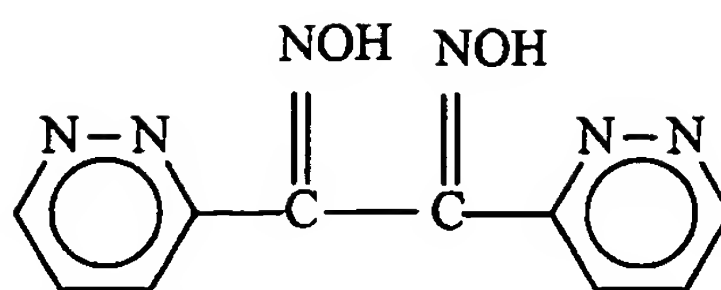
di-(1-pyrazolyl) ethanedione amphi-dioxime,



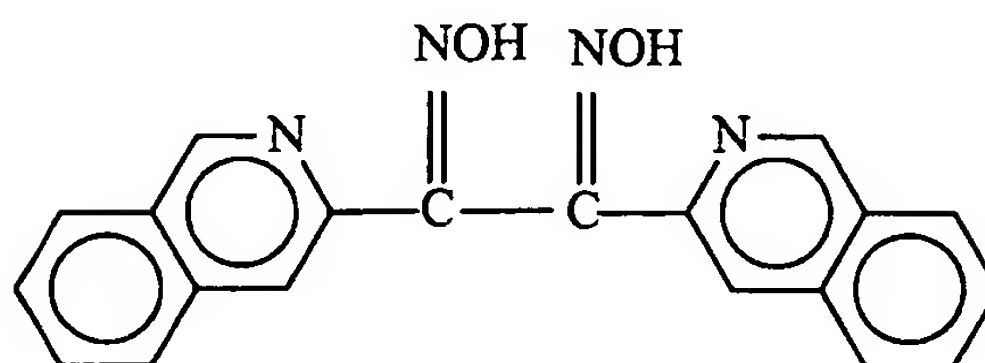
di-(2-pyrazinyl) ethanedione amphi-dioxime,



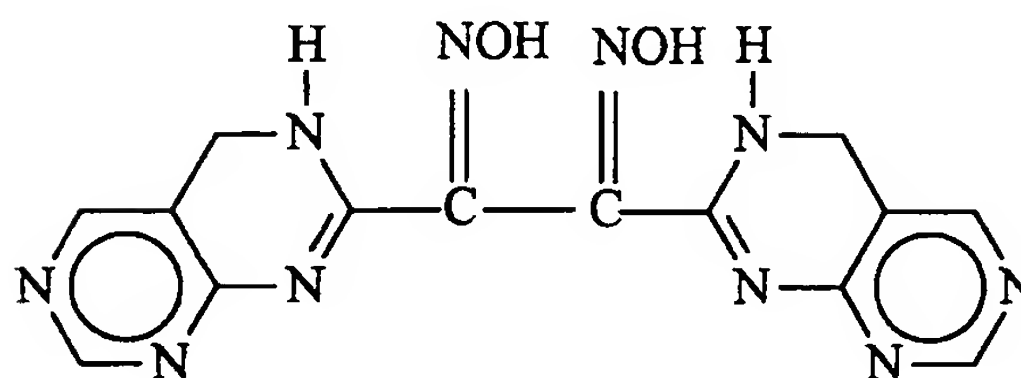
di-(2-pyrimidinyl) ethanedione amphi-dioxime,



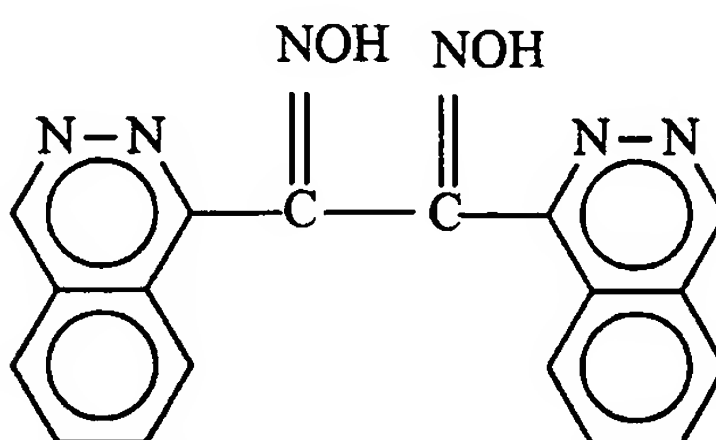
di-(3-pyridazinyl) ethanedione amphi-dioxime,



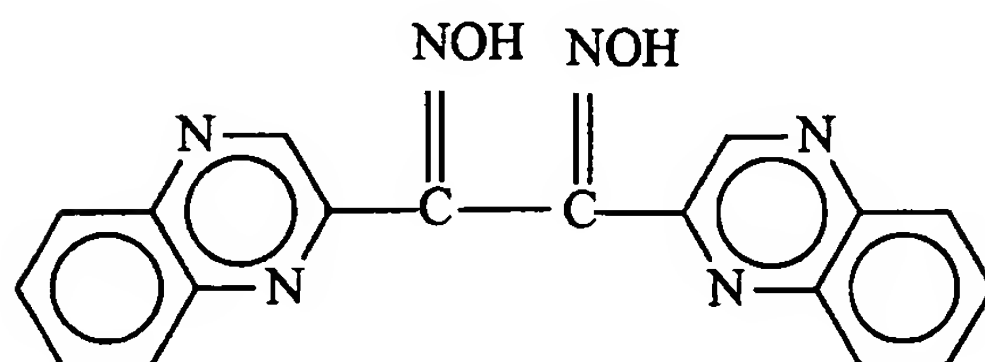
di-(3-isoquinolyl) ethanedione amphi-dioxime,



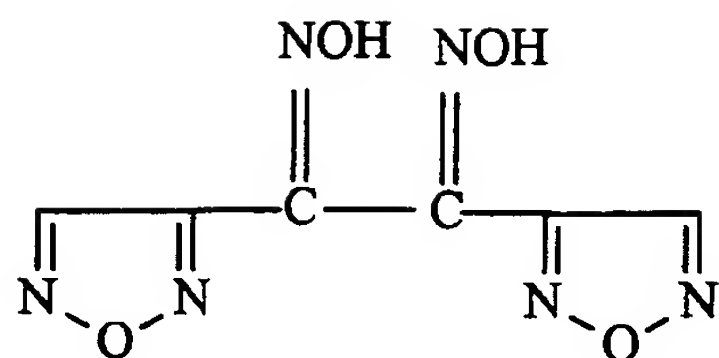
di-(8-puriny) ethanedione amphi-dioxime,



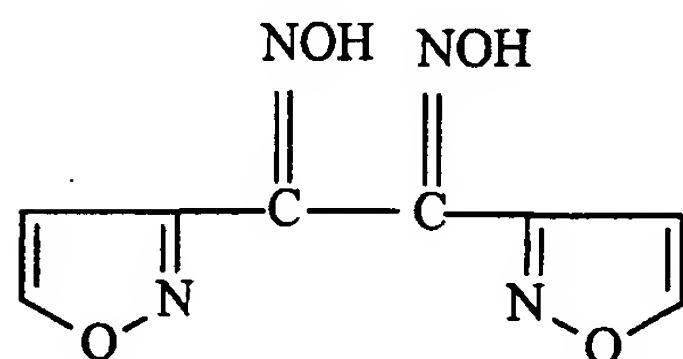
di-(1-phthalziny) ethanedione amphi-dioxime,



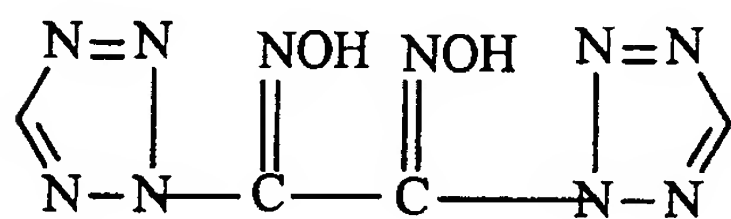
di-(2-quinoxaliny) ethanedione amphi-dioxime,



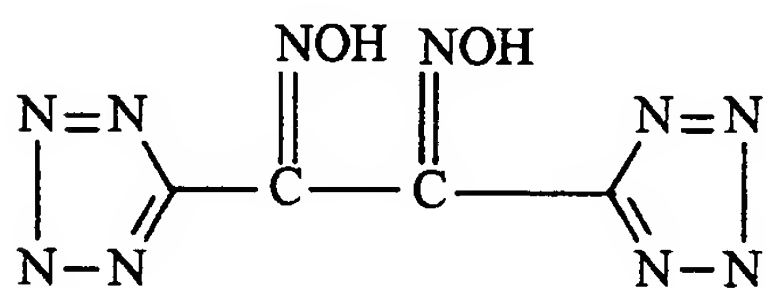
di-(3-furazanyl) ethanedione amphi-dioxime,



di-(3-isoxazolyl) ethanedione amphi-dioxime,



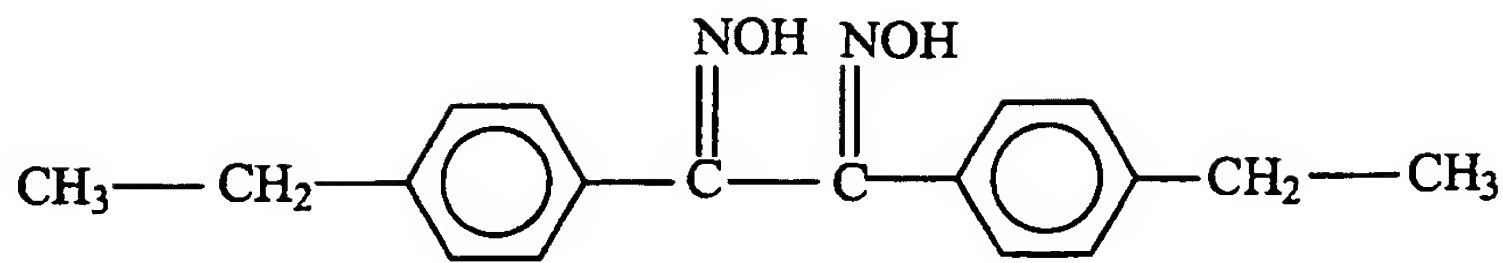
di-(2-tetrazolyl) ethanedione amphi-dioxime,



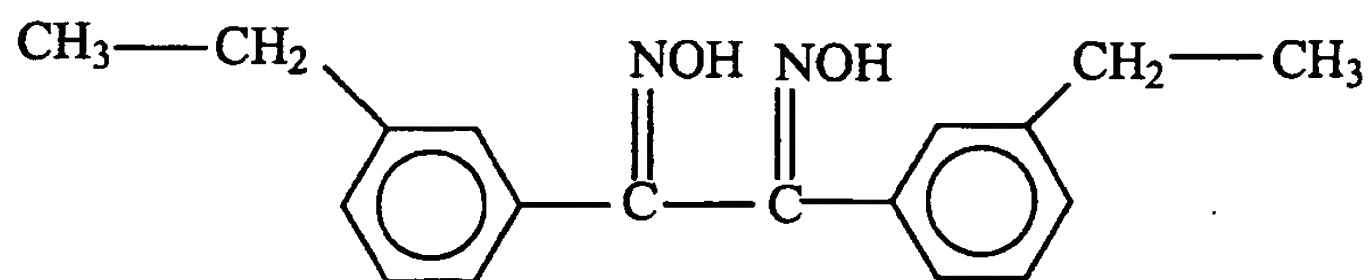
di-(5-tetrazolyl) ethanedione amphi-dioxime.

While the amphi form is preferred, mixtures of it with other forms (anti and/or syn) can be utilized, especially mixtures with approximately equal content of amphi and anti forms.

Compounds also preferred for use in the present invention include di-(4-ethylphenyl) ethanedione amphi-dioxime, di-(3-ethylphenyl) ethanedione amphi-dioxime, di-(4-propylphenyl) ethanedione amphi-dioxime, di-(2-hydroxy) ethanedione amphi-dioxime, and di-(2-hydroxy-4-ethylphenyl) ethanedione amphi-dioxime; more preferred are di-(4-ethylphenyl) ethanedione amphi-dioxime, di-(3-ethylphenyl) ethanedione amphi-dioxime, di-(4-propylphenyl) ethanedione amphi-dioxime; still more preferred is di-(4-ethylphenyl) ethanedione amphi-dioxime. While the amphi form is preferred, mixtures of it with other forms (anti and/or syn) can be utilized, especially mixtures with approximately equal content of amphi and anti forms. Representative structures include:

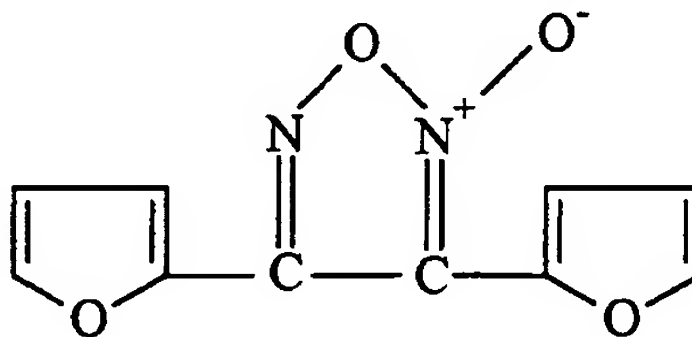


di-(4-ethylphenyl) ethanedione amphi-dioxime and



di-(3-ethylphenyl) ethanedione amphi-dioxime.

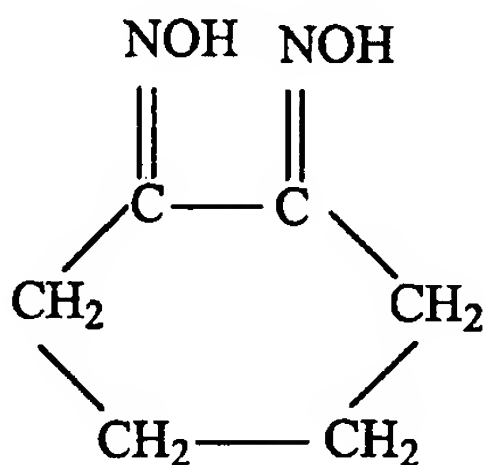
Compounds also preferred for use in the present invention include 4,5-di-(2-furyl) furoxan and 4,5-di-(2-thienyl) furoxan; preferably 4,5-di-(2-furyl) furoxan, a representative structure of which is as follows:



4,5-di-(2-furyl) furoxan,

Also preferred for incorporation in the compositions of the present invention are mixtures of any of the above compounds.

A compound also preferred for use in the present invention is amphi-1,2-cyclohexanedione, which is represented by the following structure:



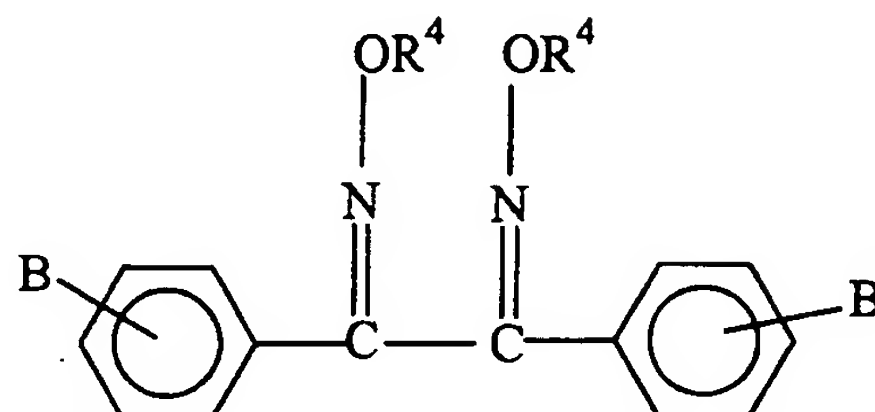
amphi-1,2-cyclohexanedione.

While the amphi form is preferred, mixtures of it with other forms (anti and/or syn) can be utilized, especially mixtures with approximately equal content of amphi and anti forms.

Also preferred for incorporation in the compositions of the present invention are mixtures of the above oxime compounds. Typically such mixtures are about half amphi-form and about half anti-form with very little (less than about 2%) syn-form. For compounds named herein, lack of designation of a particular form is non-specific and denotes either the amphi-form alone or a mixture of it with the other forms; any

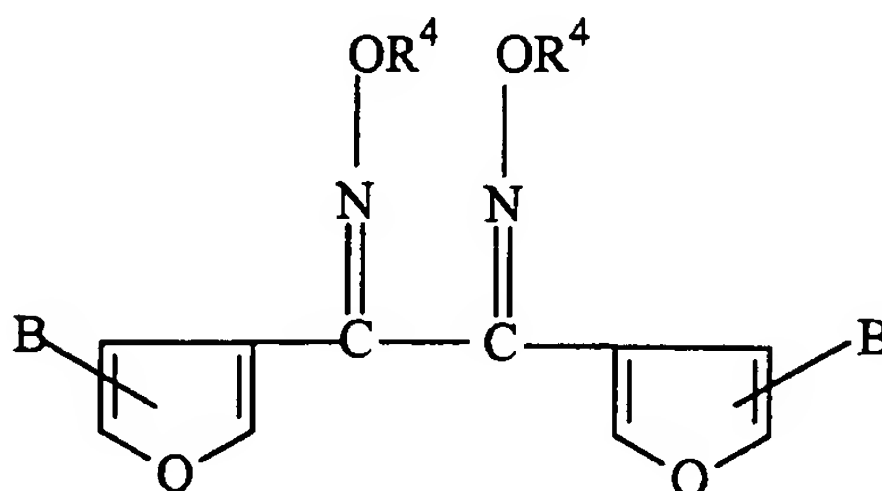
such mixture is preferably at least 40% amphi-form, more preferably at least 60% amphi-form, more preferably still at least 80% amphi-form.

Another aspect of the present invention relates to oxime compounds having the α -diamine structural formula



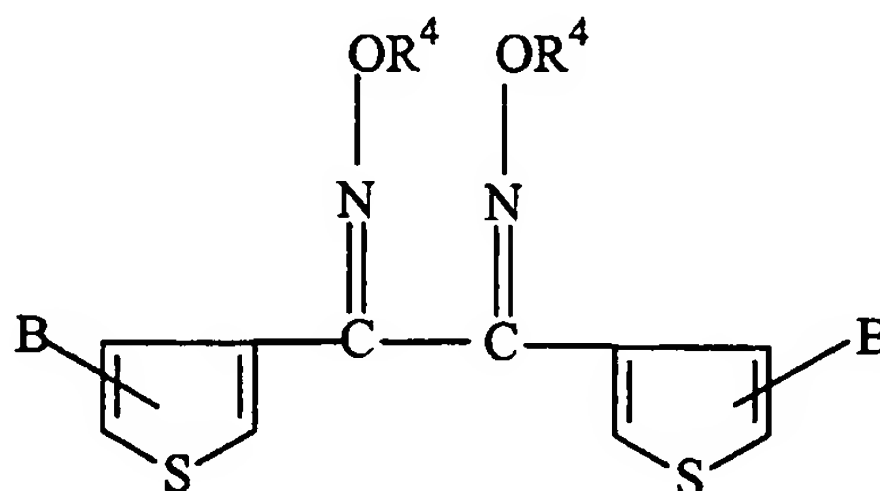
wherein -R⁴ is as defined as hereinbefore; -B is independently selected from the group consisting of alkyl, aryl, or heteroaryl; preferably alkyl; more preferably C₂-C₂₀ alkyl; more preferably a C₂-C₆ alkyl; more preferably ethyl. -B is preferably bonded to the 4-position.

Another aspect of the present invention relates to oxime compounds having the α -diamine structural formula



wherein -R⁴ and -B are as defined hereinbefore; -B is preferably bonded to the 5-position.

Another aspect of the present invention relates to oxime compounds having the structural formula:



wherein -R⁴ and -B are as defined hereinbefore; -B is preferably bonded to the 5-position.

Most preferred oxime compounds of the present invention are selected from the group consisting of di-(2-furyl) ethanedione syn-monooxime, di-(2-furyl) ethanedione anti-monooxime, di-(2-furyl) ethanedione amphi-dioxime, di-(2-furyl) ethanedione syn-dioxime, di-(2-furyl) ethanedione anti-dioxime, 1-phenyl-1,2-propanedione-2-oxime, and combinations thereof.

Compositions of this invention preferably contain from about 0.001% to about 20%, of the oxime compound, more preferably from or about 0.01% to about 10%, even more preferably from about 0.1% to about 5%, and most preferably from about 0.5% to about 5%, by weight of the composition.

Dermatologically Acceptable Carrier

The topical compositions of the present invention also comprise a dermatologically acceptable carrier for the oxime compound. The phrase "dermatologically acceptable carrier", as used herein, means that the carrier is suitable for topical application to mammalian keratinous tissue, has good aesthetic properties, is compatible with the actives of the present invention and any other components, and will not cause any untoward safety or toxicity concerns. A safe and effective amount of carrier is from about 50% to about 99.99%, preferably from about 80% to about 99.9%, more preferably from about 90% to about 98%, and most preferably from about 90% to about 95% of the composition.

The carrier can be in a wide variety of forms. For example, emulsion carriers, including, but not limited to, oil-in-water, water-in-oil, water-in-oil-in-water, and oil-in-water-in-silicone emulsions, are useful herein.

Preferred carriers comprise an emulsion such as oil-in-water emulsions, water-in-oil emulsions, and water-in-silicone emulsions. As will be understood by the skilled artisan, a given component will distribute primarily into either the water or oil/silicone phase, depending on the water solubility/dispersibility of the component in the composition. The oxime compound distributes primarily into the oil phase. Oil-in-water emulsions are especially preferred.

Emulsions according to the present invention generally contain a solution as described above and a lipid or oil. Lipids and oils may be derived from animals, plants, or petroleum and may be natural or synthetic (i.e., man-made). Preferred emulsions also contain a humectant, such as glycerin. Emulsions will preferably further contain from about 1% to about 10%, more preferably from about 2% to about 5%, of an emulsifier, based on the weight of the carrier. Emulsifiers may be nonionic, anionic or cationic. Suitable emulsifiers are disclosed in, for example, U.S. Patent 3,755,560, issued August 28, 1973, Dickert et al.; U.S. Patent 4,421,769, issued December 20, 1983, Dixon et al.; and McCutcheon's Detergents and Emulsifiers, North American Edition, pages 317-324 (1986).

The emulsion may also contain an anti-foaming agent to minimize foaming upon application to the keratinous tissue. Anti-foaming agents include high molecular weight silicones and other materials well known in the art for such use.

Suitable emulsions may have a wide range of viscosities, depending on the desired product form. Exemplary low viscosity emulsions, which are preferred, have a viscosity of about 50 centistokes or less, more preferably about 10 centistokes or less, most preferably about 5 centistokes or less.

Preferred water-in-silicone and oil-in-water emulsions are described in greater detail below.

a) Water-in-silicone emulsion

Water-in-silicone emulsions contain a continuous silicone phase and a dispersed aqueous phase.

(i) Continuous silicone phase

Preferred water-in-silicone emulsions of the present invention comprise from about 1% to about 60%, preferably from about 5% to about 40%, more preferably from about 10% to about 20%, by weight of a continuous silicone phase. The continuous silicone phase exists as an external phase that contains or surrounds the discontinuous aqueous phase described hereinafter.

The continuous silicone phase contains a polyorganosiloxane oil. A preferred water-in-silicone emulsion system is formulated to provide an oxidatively stable vehicle for the optional retinoid. The continuous silicone phase of these preferred emulsions comprises between about 50% and about 99.9% by weight of organopolysiloxane oil and less than about 50% by weight of a non-silicone oil. In an especially preferred embodiment, the continuous silicone phase comprises at least about 50%, preferably from about 60% to about 99.9%, more preferably from about 70% to about 99.9%, and even more preferably from about 80% to about 99.9%, polyorganosiloxane oil by weight of the continuous silicone phase, and up to about 50% non-silicone oils, preferably less than about 40%, more preferably less than about 30%, even more preferably less than about 10%, and most preferably less than about 2%, by weight of the continuous silicone phase. Concentrations of non-silicone oils in the continuous silicone phase are minimized or avoided altogether so as to further enhance oxidative stability of the selected retinoid in the compositions. Water-in-silicone emulsions of this type are described in copending U.S. Patent Application Serial No. 08/570,275, filed December 11, 1995, in the names of Joseph Michael Zukowski, Brent William Mason, Larry Richard Robinson and Greg George Hillebrand.

The organopolysiloxane oil for use in the composition may be volatile, non-volatile, or a mixture of volatile and non-volatile silicones. The term "nonvolatile" as used in this context refers to those silicones that are liquid under ambient conditions and have a flash point (under one atmospheric of pressure) of or greater than about 100°C. The term "volatile" as used in this context refers to all other silicone oils. Suitable organopolysiloxanes can be selected from a wide variety of silicones spanning a broad range of volatilities and viscosities. Examples of suitable organopolysiloxane oils include polyalkylsiloxanes, cyclic polyalkylsiloxanes, and polyalkylarylsiloxanes.

Polyalkylsiloxanes useful in the composition herein include polyalkylsiloxanes with viscosities of from about 0.5 to about 1,000,000 centistokes at 25°C. Such polyalkylsiloxanes can be represented by the general chemical formula $R_3SiO[R_2SiO]_xSiR_3$ wherein R is an alkyl group having from one to about 30 carbon atoms (preferably R is methyl or ethyl, more preferably methyl; also mixed alkyl groups can be used in the same molecule), and x is an integer from 0 to about 10,000, chosen to achieve the desired molecular weight which can range to over about 10,000,000. Commercially available polyalkylsiloxanes include the polydimethylsiloxanes, which are also known as dimethicones, examples of which include the Vicasil® series sold by General Electric Company and the Dow Corning® 200 series sold by Dow Corning Corporation. Specific examples of suitable polydimethylsiloxanes include Dow Corning® 200 fluid having a viscosity of 0.65 centistokes and a boiling point of 100°C, Dow Corning® 225 fluid having a viscosity of

10 centistokes and a boiling point greater than 200°C, and Dow Corning® 200 fluids having viscosities of 50, 350, and 12,500 centistokes, respectively, and boiling points greater than 200°C. Suitable dimethicones include those represented by the chemical formula $(\text{CH}_3)_3\text{SiO}[(\text{CH}_3)_2\text{SiO}]_x[\text{CH}_3\text{RSiO}]_y\text{Si}(\text{CH}_3)_3$ wherein R is straight or branched chain alkyl having from two to about 30 carbon atoms and x and y are each integers of 1 or greater selected to achieve the desired molecular weight which can range to over about 10,000,000. Examples of these alkyl-substituted dimethicones include cetyl dimethicone and lauryl dimethicone.

Cyclic polyalkylsiloxanes suitable for use in the composition include those represented by the chemical formula $[\text{SiR}_2\text{-O}]_n$ wherein R is an alkyl group (preferably R is methyl or ethyl, more preferably methyl) and n is an integer from about 3 to about 8, more preferably n is an integer from about 3 to about 7, and most preferably n is an integer from about 4 to about 6. When R is methyl, these materials are typically referred to as cyclomethicones. Commercially available cyclomethicones include Dow Corning® 244 fluid having a viscosity of 2.5 centistokes, and a boiling point of 172°C, which primarily contains the cyclomethicone tetramer (i.e. n=4), Dow Corning® 344 fluid having a viscosity of 2.5 centistokes and a boiling point of 178°C, which primarily contains the cyclomethicone pentamer (i.e. n=5), Dow Corning® 245 fluid having a viscosity of 4.2 centistokes and a boiling point of 205°C, which primarily contains a mixture of the cyclomethicone tetramer and pentamer (i.e. n=4 and 5), and Dow Corning® 345 fluid having a viscosity of 4.5 centistokes and a boiling point of 217°, which primarily contains a mixture of the cyclomethicone tetramer, pentamer, and hexamer (i.e. n=4, 5, and 6).

Also useful are materials such as trimethylsiloxysilicate, which is a polymeric material corresponding to the general chemical formula $[(\text{CH}_3)_3\text{SiO}_{1/2}]_x[\text{SiO}_2]_y$, wherein x is an integer from about 1 to about 500 and y is an integer from about 1 to about 500. A commercially available trimethylsiloxysilicate is sold as a mixture with dimethicone as Dow Corning® 593 fluid.

Dimethiconols are also suitable for use in the composition. These compounds can be represented by the chemical formulas $\text{R}_3\text{SiO}[\text{R}_2\text{SiO}]_x\text{SiR}_2\text{OH}$ and $\text{HOR}_2\text{SiO}[\text{R}_2\text{SiO}]_x\text{SiR}_2\text{OH}$ wherein R is an alkyl group (preferably R is methyl or ethyl, more preferably methyl) and x is an integer from 0 to about 500, chosen to achieve the desired molecular weight. Commercially available dimethiconols are typically sold as mixtures with dimethicone or cyclomethicone (e.g. Dow Corning® 1401, 1402, and 1403 fluids).

Polyalkylaryl siloxanes are also suitable for use in the composition. Polymethylphenyl siloxanes having viscosities from about 15 to about 65 centistokes at 25°C are especially useful.

Preferred for use herein are organopolysiloxanes selected from the group consisting of polyalkylsiloxanes, alkyl substituted dimethicones, cyclomethicones, trimethylsiloxysilicates, dimethiconols, polyalkylaryl siloxanes, and mixtures thereof. More preferred for use herein are polyalkylsiloxanes and cyclomethicones. Preferred among the polyalkylsiloxanes are dimethicones.

As stated above, the continuous silicone phase may contain one or more non-silicone oils. Suitable non-silicone oils have a melting point of about 25°C or less under about one atmosphere of pressure.

Examples of non-silicone oils suitable for use in the continuous silicone phase are those well known in the chemical arts in topical personal care products in the form of water-in-oil emulsions, e.g., mineral oil, vegetable oils, synthetic oils, semisynthetic oils, etc..

(ii) Dispersed aqueous phase

The topical compositions of the present invention comprise from about 30% to about 90%, more preferably from about 50% to about 85%, and most preferably from about 70% to about 80% of a dispersed aqueous phase. In emulsion technology, the term "dispersed phase" is a term well-known to one skilled in the art which means that the phase exists as small particles or droplets that are suspended in and surrounded by a continuous phase. The dispersed phase is also known as the internal or discontinuous phase. The dispersed aqueous phase is a dispersion of small aqueous particles or droplets suspended in and surrounded by the continuous silicone phase described hereinbefore.

The aqueous phase can be water, or a combination of water and one or more water soluble or dispersible ingredients. Nonlimiting examples of such optional ingredients include thickeners, acids, bases, salts, chelants, gums, water-soluble or dispersible alcohols and polyols, buffers, preservatives, sunscreens, agents, colorings, and the like.

The topical compositions of the present invention will typically comprise from about 25% to about 90%, preferably from about 40% to about 80%, more preferably from about 60% to about 80%, water in the dispersed aqueous phase by weight of the composition.

(iii) Emulsifier for dispersing the aqueous phase

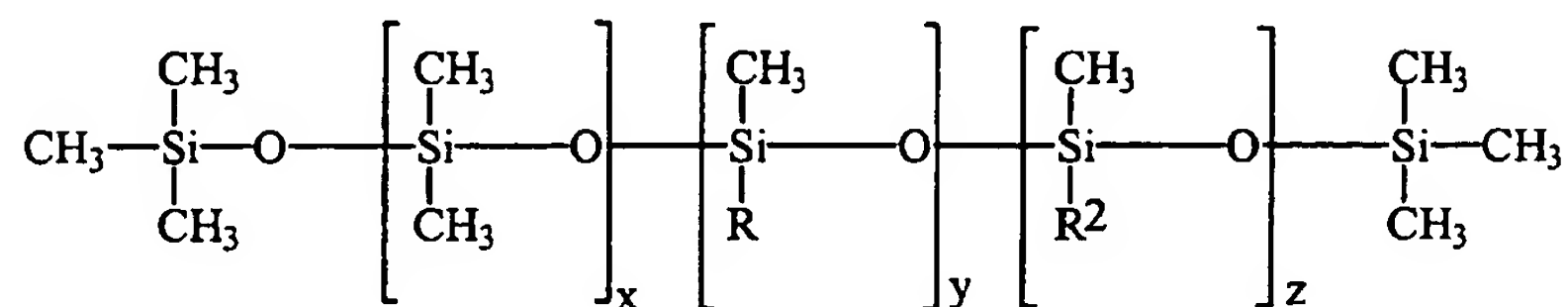
The water-in-silicone emulsions of the present invention preferably comprise an emulsifier. In a preferred embodiment, the composition contains from about 0.1% to about 10% emulsifier, more preferably from about 0.5% to about 7.5%, most preferably from about 1% to about 5%, emulsifier by weight of the composition. The emulsifier helps disperse and suspend the aqueous phase within the continuous silicone phase.

A wide variety of emulsifying agents can be employed herein to form the preferred water-in-silicone emulsion. Known or conventional emulsifying agents can be used in the composition, provided that the selected emulsifying agent is chemically and physically compatible with essential components of the composition, and provides the desired dispersion characteristics. Suitable emulsifiers include silicone emulsifiers, non-silicon-containing emulsifiers, and mixtures thereof, known by those skilled in the art for use in topical personal care products. Preferably these emulsifiers have an HLB value of or less than about 14, more preferably from about 2 to about 14, and most preferably from about 4 to about 14. Emulsifiers having an HLB value outside of these ranges can be used in combination with other emulsifiers to achieve an effective weighted average HLB for the combination that falls within these ranges.

Silicone emulsifiers are preferred. A wide variety of silicone emulsifiers are useful herein. These silicone emulsifiers are typically organically modified organopolysiloxanes, also known to those skilled in the art as silicone surfactants. Useful silicone emulsifiers include dimethicone copolyols. These materials are polydimethyl siloxanes which have been modified to include polyether side chains such as polyethylene

oxide chains, polypropylene oxide chains, mixtures of these chains, and polyether chains containing moieties derived from both ethylene oxide and propylene oxide. Other examples include alkyl-modified dimethicone copolyols, i.e., compounds which contain C2-C30 pendant side chains. Still other useful dimethicone copolyols include materials having various cationic, anionic, amphoteric, and zwitterionic pendant moieties.

The dimethicone copolyol emulsifiers useful herein can be described by the following general structure:



wherein R is C1-C30 straight, branched, or cyclic alkyl and R² is selected from the group consisting of

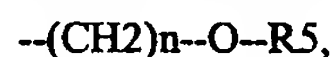


and



wherein n is an integer from 3 to about 10; R³ and R⁴ are selected from the group consisting of H and C1-C6 straight or branched chain alkyl such that R³ and R⁴ are not simultaneously the same; and m, o, x, and y are selected such that the molecule has an overall molecular weight from about 200 to about 10,000,000, with m, o, x, and y being independently selected from integers of zero or greater such that m and o are not both simultaneously zero, and z being independently selected from integers of 1 or greater. It is recognized that positional isomers of these copolyols can be achieved. The chemical representations depicted above for the R² moieties containing the R³ and R⁴ groups are not meant to be limiting but are shown as such for convenience.

Also useful herein, although not strictly classified as dimethicone copolyols, are silicone surfactants as depicted in the structures in the previous paragraph wherein R² is:



wherein R⁵ is a cationic, anionic, amphoteric, or zwitterionic moiety.

Nonlimiting examples of dimethicone copolyols and other silicone surfactants useful as emulsifiers herein include polydimethylsiloxane polyether copolymers with pendant polyethylene oxide sidechains, polydimethylsiloxane polyether copolymers with pendant polypropylene oxide sidechains, polydimethylsiloxane polyether copolymers with pendant mixed polyethylene oxide and polypropylene oxide sidechains, polydimethylsiloxane polyether copolymers with pendant mixed poly(ethylene)(propylene)oxide sidechains, polydimethylsiloxane polyether copolymers with pendant organobetaine sidechains, polydimethylsiloxane polyether copolymers with pendant carboxylate sidechains, polydimethylsiloxane polyether copolymers with pendant quaternary ammonium sidechains; and also further modifications of the preceding copolymers containing pendant C2-C30 straight, branched, or cyclic alkyl

moieties. Examples of commercially available dimethicone copolyols useful herein sold by Dow Corning Corporation are Dow Corning® 190, 193, Q2-5220, 2501 Wax, 2-5324 fluid, and 3225C (this later material being sold as a mixture with cyclomethicone). Cetyl dimethicone copolyol is commercially available as a mixture with polyglyceryl-4 isostearate (and) hexyl laurate and is sold under the tradename ABIL® WE-09 (available from Goldschmidt). Cetyl dimethicone copolyol is also commercially available as a mixture with hexyl laurate (and) polyglyceryl-3 oleate (and) cetyl dimethicone and is sold under the tradename ABIL® WS-08 (also available from Goldschmidt). Other nonlimiting examples of dimethicone copolyols also include lauryl dimethicone copolyol, dimethicone copolyol acetate, diemethicone copolyol adipate, dimethicone copolyolamine, dimethicone copolyol behenate, dimethicone copolyol butyl ether, dimethicone copolyol hydroxy stearate, dimethicone copolyol isostearate, dimethicone copolyol laurate, dimethicone copolyol methyl ether, dimethicone copolyol phosphate, and dimethicone copolyol stearate. See International Cosmetic Ingredient Dictionary, Fifth Edition, 1993.

Dimethicone copolyol emulsifiers useful herein are described, for example, in U.S. Patent No. 4,960,764, to Figueroa, Jr. et al., issued October 2, 1990; European Patent No. EP 330,369, to SanoGueira, published August 30, 1989; G.H. Dahms, et al., "New Formulation Possibilities Offered by Silicone Copolyols," *Cosmetics & Toiletries*, vol. 110, pp. 91-100, March 1995; M.E. Carlotti et al., "Optimization of W/O-S Emulsions And Study Of The Quantitative Relationships Between Ester Structure And Emulsion Properties," *J. Dispersion Science And Technology*, 13(3), 315-336 (1992); P. Hameyer, "Comparative Technological Investigations of Organic and Organosilicone Emulsifiers in Cosmetic Water-in-Oil Emulsion Preparations," *HAPPI* 28(4), pp. 88-128 (1991); J. Smid-Korbar et al., "Efficiency and usability of silicone surfactants in emulsions," *Provisional Communication, International Journal of Cosmetic Science*, 12, 135-139 (1990); and D.G. Krzysik et al., "A New Silicone Emulsifier For Water-in-Oil Systems," *Drug and Cosmetic Industry*, vol. 146(4) pp. 28-81 (April 1990).

Among the non-silicone-containing emulsifiers useful herein are various non-ionic and anionic emulsifying agents such as sugar esters and polyesters, alkoxylated sugar esters and polyesters, C1-C30 fatty acid esters of C1-C30 fatty alcohols, alkoxylated derivatives of C1-C30 fatty acid esters of C1-C30 fatty alcohols, alkoxylated ethers of C1-C30 fatty alcohols, polyglyceryl esters of C1-C30 fatty acids, C1-C30 esters of polyols, C1-C30 ethers of polyols, alkyl phosphates, polyoxyalkylene fatty ether phosphates, fatty acid amides, acyl lactylates, soaps, and mixtures thereof. Other suitable emulsifiers are described, for example, in McCutcheon's, *Detergents and Emulsifiers*, North American Edition (1986), published by Allured Publishing Corporation; U.S. Patent No. 5,011,681 to Ciotti et al., issued April 30, 1991; U.S. Patent No. 4,421,769 to Dixon et al., issued December 20, 1983; and U.S. Patent No. 3,755,560 to Dickert et al., issued August 28, 1973.

Nonlimiting examples of these non-silicone-containing emulsifiers include: polyethylene glycol 20 sorbitan monolaurate (Polysorbate 20), polyethylene glycol 5 soya sterol, Steareth-20, Ceteareth-20, PPG-2 methyl glucose ether distearate, Ceteth-10, Polysorbate 80, cetyl phosphate, potassium cetyl phosphate, diethanolamine cetyl phosphate, Polysorbate 60, glyceryl stearate, PEG-100 stearate, polyoxyethylene 20

sorbitan trioleate (Polysorbate 85), sorbitan monolaurate, polyoxyethylene 4 lauryl ether sodium stearate, polyglyceryl-4 isostearate, hexyl laurate, steareth-20, cetareth-20, PPG-2 methyl glucose ether distearate, ceteth-10, diethanolamine cetyl phosphate, glyceryl stearate, PEG-100 stearate, and mixtures thereof.

b) Oil-in-Water Emulsions

Other preferred topical carriers include oil-in-water emulsions, having a continuous aqueous phase and a hydrophobic, water-insoluble phase ("oil phase") dispersed therein. Examples of suitable carriers comprising oil-in-water emulsions are described in U.S. Pat. No. 5,073,371, to Turner, D.J. et al., issued Dec. 17, 1991, and U.S. Pat. No. 5,073,372, to Turner, D.J. et al., issued Dec. 17, 1991. An especially preferred oil-in-water emulsion, containing a structuring agent, hydrophilic surfactant and water, is described in detail hereinafter.

(i) Structuring Agent

A preferred oil-in-water emulsion comprises a structuring agent to assist in the formation of a liquid crystalline gel network structure. Without being limited by theory, it is believed that the structuring agent assists in providing rheological characteristics to the composition which contribute to the stability of the composition. The structuring agent may also function as an emulsifier or surfactant. Preferred compositions of this invention comprise from about 0.5% to about 20%, more preferably from about 1% to about 10%, most preferably from about 1% to about 5%, by weight of the composition, of a structuring agent.

The preferred structuring agents of the present invention are selected from the group consisting of stearic acid, palmitic acid, stearyl alcohol, cetyl alcohol, behenyl alcohol, stearic acid, palmitic acid, the polyethylene glycol ether of stearyl alcohol having an average of about 1 to about 21 ethylene oxide units, the polyethylene glycol ether of cetyl alcohol having an average of about 1 to about 5 ethylene oxide units, and mixtures thereof. More preferred structuring agents of the present invention are selected from the group consisting of stearyl alcohol, cetyl alcohol, behenyl alcohol, the polyethylene glycol ether of stearyl alcohol having an average of about 2 ethylene oxide units (steareth-2), the polyethylene glycol ether of stearyl alcohol having an average of about 21 ethylene oxide units (steareth-21), the polyethylene glycol ether of cetyl alcohol having an average of about 2 ethylene oxide units, and mixtures thereof. Even more preferred structuring agents are selected from the group consisting of stearic acid, palmitic acid, stearyl alcohol, cetyl alcohol, behenyl alcohol, steareth-2, steareth-21, and mixtures thereof.

(ii) Hydrophilic surfactant

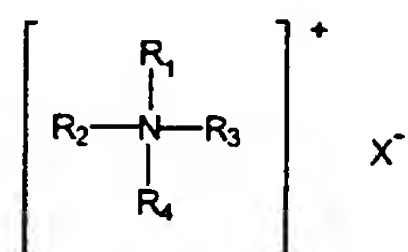
The preferred oil-in-water emulsions comprise from about 0.05% to about 10%, preferably from about 1% to about 6%, and more preferably from about 1% to about 3% of at least one hydrophilic surfactant which can disperse the hydrophobic materials in the water phase (percentages by weight of the topical carrier). The surfactant, at a minimum, must be hydrophilic enough to disperse in water.

Suitable surfactants include any of a wide variety of known cationic, anionic, zwitterionic, and amphoteric surfactants. See, McCutcheon's, Detergents and Emulsifiers, North American Edition (1986),

published by Allured Publishing Corporation; U.S. Patent 5,011,681; U.S. Patent 4,421,769; and U.S. Patent 3,755,560; these references are incorporated herein by reference in their entirety.

The exact surfactant chosen will depend upon the pH of the composition and the other components present.

Preferred are cationic surfactants, especially dialkyl quaternary ammonium compounds, examples of which are described in U.S. Patent 5,151,209; U.S. Patent 5,151,210; U.S. Patent 5,120,532; U.S. Patent 4,387,090; U.S. Patent 3,155,591; U.S. Patent 3,929,678; U.S. Patent 3,959,461; McCutcheon's, Detergents & Emulsifiers, (North American edition 1979) M.C. Publishing Co.; and Schwartz, et al., Surface Active Agents, Their Chemistry and Technology, New York: Interscience Publishers, 1949; which descriptions are incorporated herein by reference. The cationic surfactants useful herein include cationic ammonium salts such as those having the formula:



wherein R1, is an alkyl group having from about 12 to about 30 carbon atoms, or an aromatic, aryl or alkaryl group having from about 12 to about 30 carbon atoms; R2, R3, and R4 are independently selected from hydrogen, an alkyl group having from about 1 to about 22 carbon atoms, or aromatic, aryl or alkaryl groups having from about 12 to about 22 carbon atoms; and X is any compatible anion, preferably selected from the group consisting of chloride, bromide, iodide, acetate, phosphate, nitrate, sulfate, methyl sulfate, ethyl sulfate, tosylate, lactate, citrate, glycolate, and mixtures thereof. Additionally, the alkyl groups of R1, R2, R3, and R4 can also contain ester and/or ether linkages, or hydroxy or amino group substituents (e.g., the alkyl groups can contain polyethylene glycol and polypropylene glycol moieties).

More preferably, R1 is an alkyl group having from about 12 to about 22 carbon atoms; R2 is selected from H or an alkyl group having from about 1 to about 22 carbon atoms; R3 and R4 are independently selected from H or an alkyl group having from about 1 to about 3 carbon atoms; and X is as described previously.

Most preferably, R1 is an alkyl group having from about 12 to about 22 carbon atoms; R2, R3, and R4 are selected from H or an alkyl group having from about 1 to about 3 carbon atoms; and X is as described previously.

Alternatively, other useful cationic emulsifiers include amino-amides, wherein in the above structure R1 is alternatively R5CONH-(CH₂)_n, wherein R5 is an alkyl group having from about 12 to about 22 carbon atoms, and n is an integer from about 2 to about 6, more preferably from about 2 to about 4, and most preferably from about 2 to about 3. Nonlimiting examples of these cationic emulsifiers include stearamidopropyl PG-dimonium chloride phosphate, behenamidopropyl PG dimonium chloride, stearamidopropyl ethyldimonium ethosulfate, stearamidopropyl dimethyl (myristyl acetate) ammonium chloride, stearamidopropyl dimethyl cetaryl ammonium tosylate, stearamidopropyl dimethyl ammonium

chloride, stearamidopropyl dimethyl ammonium lactate, and mixtures thereof. Especially preferred is behenamidopropyl PG dimonium chloride.

Nonlimiting examples of quaternary ammonium salt cationic surfactants include those selected from the group consisting of cetyl ammonium chloride, cetyl ammonium bromide, lauryl ammonium chloride, lauryl ammonium bromide, stearyl ammonium chloride, stearyl ammonium bromide, cetyl dimethyl ammonium chloride, cetyl dimethyl ammonium bromide, lauryl dimethyl ammonium chloride, lauryl dimethyl ammonium bromide, stearyl dimethyl ammonium chloride, stearyl dimethyl ammonium bromide, cetyl trimethyl ammonium chloride, cetyl trimethyl ammonium bromide, lauryl trimethyl ammonium chloride, lauryl trimethyl ammonium bromide, stearyl trimethyl ammonium chloride, stearyl trimethyl ammonium bromide, lauryl dimethyl ammonium chloride, stearyl dimethyl cetyl ditallow dimethyl ammonium chloride, dicetyl ammonium chloride, dicetyl ammonium bromide, dilauryl ammonium chloride, dilauryl ammonium bromide, distearyl ammonium chloride, distearyl ammonium bromide, dicetyl methyl ammonium chloride, dicetyl methyl ammonium bromide, dilauryl methyl ammonium chloride, dilauryl methyl ammonium bromide, distearyl methyl ammonium chloride, distearyl methyl ammonium bromide, and mixtures thereof. Additional quaternary ammonium salts include those wherein the C12 to C30 alkyl carbon chain is derived from a tallow fatty acid or from a coconut fatty acid. The term "tallow" refers to an alkyl group derived from tallow fatty acids (usually hydrogenated tallow fatty acids), which generally have mixtures of alkyl chains in the C16 to C18 range. The term "coconut" refers to an alkyl group derived from a coconut fatty acid, which generally have mixtures of alkyl chains in the C12 to C14 range. Examples of quaternary ammonium salts derived from these tallow and coconut sources include ditallow dimethyl ammonium chloride, ditallow dimethyl ammonium methyl sulfate, di(hydrogenated tallow) dimethyl ammonium chloride, di(hydrogenated tallow) dimethyl ammonium acetate, ditallow dipropyl ammonium phosphate, ditallow dimethyl ammonium nitrate, di(coconutalkyl)dimethyl ammonium chloride, di(coconutalkyl)dimethyl ammonium bromide, tallow ammonium chloride, coconut ammonium chloride, stearamidopropyl PG-dimonium chloride phosphate, stearamidopropyl ethyldimonium ethosulfate, stearamidopropyl dimethyl (myristyl acetate) ammonium chloride, stearamidopropyl dimethyl cetearyl ammonium tosylate, stearamidopropyl dimethyl ammonium chloride, stearamidopropyl dimethyl ammonium lactate, and mixtures thereof. An example of a quaternary ammonium compound having an alkyl group with an ester linkage is ditallowyl oxyethyl dimethyl ammonium chloride.

More preferred cationic surfactants are those selected from the group consisting of behenamidopropyl PG dimonium chloride, dilauryl dimethyl ammonium chloride, distearyl dimethyl ammonium chloride, dimyristyl dimethyl ammonium chloride, dipalmityl dimethyl ammonium chloride, distearyl dimethyl ammonium chloride, stearamidopropyl PG-dimonium chloride phosphate, stearamidopropyl ethyldiammonium ethosulfate, stearamidopropyl dimethyl (myristyl acetate) ammonium chloride, stearamidopropyl dimethyl cetearyl ammonium tosylate, stearamidopropyl dimethyl ammonium chloride, stearamidopropyl dimethyl ammonium lactate, and mixtures thereof.

Most preferred cationic surfactants are those selected from the group consisting of behenamidopropyl PG dimonium chloride, dilauryl dimethyl ammonium chloride, distearyl dimethyl ammonium chloride, dimyristyl dimethyl ammonium chloride, dipalmityl dimethyl ammonium chloride, and mixtures thereof.

A preferred combination of cationic surfactant and structuring agent is behenamidopropyl PG dimonium chloride and/or behenyl alcohol, wherein the ratio is preferably optimized to maintained to enhance physical and chemical stability, especially when such a combination contains ionic and/or highly polar solvents. This combination is especially useful for delivery of sunscreens agents such as zinc oxide and octyl methoxycinnamate.

A wide variety of anionic surfactants are also useful herein. See, e.g., U.S. Patent No. 3,929,678, to Laughlin et al., issued December 30, 1975, which is incorporated herein by reference in its entirety. Nonlimiting examples of anionic surfactants include the alkoyl isethionates, and the alkyl and alkyl ether sulfates. The alkoyl isethionates typically have the formula $\text{RCO-OCH}_2\text{CH}_2\text{SO}_3\text{M}$ wherein R is alkyl or alkenyl of from about 10 to about 30 carbon atoms, and M is a water-soluble cation such as ammonium, sodium, potassium and triethanolamine. Nonlimiting examples of these isethionates include those alkoyl isethionates selected from the group consisting of ammonium cocoyl isethionate, sodium cocoyl isethionate, sodium lauroyl isethionate, sodium stearyl isethionate, and mixtures thereof.

The alkyl and alkyl ether sulfates typically have the respective formulae ROSO_3M and $\text{RO}(\text{C}_2\text{H}_4\text{O})_x\text{SO}_3\text{M}$, wherein R is alkyl or alkenyl of from about 10 to about 30 carbon atoms, x is from about 1 to about 10, and M is a water-soluble cation such as ammonium, sodium, potassium and triethanolamine. Another suitable class of anionic surfactants are the water-soluble salts of the organic, sulfuric acid reaction products of the general formula:



wherein R1 is chosen from the group consisting of a straight or branched chain, saturated aliphatic hydrocarbon radical having from about 8 to about 24, preferably about 10 to about 16, carbon atoms; and M is a cation. Still other anionic synthetic surfactants include the class designated as succinamates, olefin sulfonates having about 12 to about 24 carbon atoms, and β -alkyloxy alkane sulfonates. Examples of these materials are sodium lauryl sulfate and ammonium lauryl sulfate.

Other anionic materials useful herein are soaps (i.e. alkali metal salts, e.g., sodium or potassium salts) of fatty acids, typically having from about 8 to about 24 carbon atoms, preferably from about 10 to about 20 carbon atoms. The fatty acids used in making the soaps can be obtained from natural sources such as, for instance, plant or animal-derived glycerides (e.g., palm oil, coconut oil, soybean oil, castor oil, tallow, lard, etc.) The fatty acids can also be synthetically prepared. Soaps are described in more detail in U.S. Patent No. 4,557,853.

Amphoteric and zwitterionic surfactants are also useful herein. Examples of amphoteric and zwitterionic surfactants which can be used in the compositions of the present invention are those which are broadly described as derivatives of aliphatic secondary and tertiary amines in which the aliphatic radical can

be straight or branched chain and wherein one of the aliphatic substituents contains from about 8 to about 22 carbon atoms (preferably C8 - C18) and one contains an anionic water solubilizing group, e.g., carboxy, sulfonate, sulfate, phosphate, or phosphonate. Examples are alkyl imino acetates, and iminodialkanoates and aminoalkanoates of the formulas $RN[CH_2]_mCO_2M$ and $RNH(CH_2)_mCO_2M$ wherein m is from 1 to 4, R is a C8-C22 alkyl or alkenyl, and M is H, alkali metal, alkaline earth metal ammonium, or alkanolammonium. Also included are imidazolinium and ammonium derivatives. Specific examples of suitable amphoteric surfactants include sodium 3-dodecyl-aminopropionate, sodium 3-dodecylaminopropane sulfonate, N-alkyltaurines such as the one prepared by reacting dodecylamine with sodium isethionate according to the teaching of U.S. Patent 2,658,072 which is incorporated herein by reference in its entirety; N-higher alkyl aspartic acids such as those produced according to the teaching of U.S. Patent 2,438,091 which is incorporated herein by reference in its entirety; and the products sold under the trade name "Miranol" and described in U.S. Patent 2,528,378, which is incorporated herein by reference in its entirety. Other examples of useful amphoterics include phosphates, such as coamidopropyl PG-dimonium chloride phosphate (commercially available as Monaquat PTC, from Mona Corp.).

Also useful herein as amphoteric or zwitterionic surfactants are the betaines. Examples of betaines include the higher alkyl betaines, such as coco dimethyl carboxymethyl betaine, lauryl dimethyl carboxymethyl betaine, lauryl dimethyl alphacarboxyethyl betaine, cetyl dimethyl carboxymethyl betaine, cetyl dimethyl betaine (available as Lonzone 16SP from Lonza Corp.), lauryl bis-(2-hydroxyethyl) carboxymethyl betaine, stearyl bis-(2-hydroxypropyl) carboxymethyl betaine, oleyl dimethyl gamma-carboxypropyl betaine, lauryl bis-(2-hydroxypropyl)alpha-carboxyethyl betaine, coco dimethyl sulfopropyl betaine, stearyl dimethyl sulfopropyl betaine, lauryl dimethyl sulfoethyl betaine, lauryl bis-(2-hydroxyethyl) sulfopropyl betaine, and amidobetaines and amidosulfobetaines (wherein the $RCONH(CH_2)_3$ radical is attached to the nitrogen atom of the betaine), oleyl betaine (available as amphoteric Velvetex OLB-50 from Henkel), and cocamidopropyl betaine (available as Velvetex BK-35 and BA-35 from Henkel).

Other useful amphoteric and zwitterionic surfactants include the sultaines and hydroxysultaines such as cocamidopropyl hydroxysultaine (available as Mirataine CBS from Rhone-Poulenc), and the alkanoyl sarcosinates corresponding to the formula $RCON(CH_3)CH_2CH_2CO_2M$ wherein R is alkyl or alkenyl of about 10 to about 20 carbon atoms, and M is a water-soluble cation such as ammonium, sodium, potassium and trialkanolamine (e.g., triethanolamine), a preferred example of which is sodium lauroyl sarcosinate.

(iii) Water

The preferred oil-in-water emulsion comprises from about 25% to about 98%, preferably from about 65% to about 95%, more preferably from about 70% to about 90% water by weight of the topical carrier.

The hydrophobic phase is dispersed in the continuous aqueous phase. The hydrophobic phase may contain water insoluble or partially soluble materials such as are known in the art, including but not limited

to the silicones described herein in reference to silicone-in-water emulsions, and other oils and lipids such as described above in reference to emulsions.

The topical compositions of the subject invention, including but not limited to lotions and creams, may comprise a dermatologically acceptable emollient. Such compositions preferably contain from about 2% to about 50% of the emollient. As used herein, "emollient" refers to a material useful for the prevention or relief of dryness, as well as for the protection of the skin. A wide variety of suitable emollients are known and may be used herein. Sagarin, *Cosmetics, Science and Technology*, 2nd Edition, Vol. 1, pp. 32-43 (1972), incorporated herein by reference, contains numerous examples of materials suitable as an emollient. A preferred emollient is glycerin. Glycerin is preferably used in an amount of from or about 0.001 to or about 20%, more preferably from or about 0.01 to or about 10%, most preferably from or about 0.1 to or about 5%, e.g., 3%.

Lotions and creams according to the present invention generally comprise a solution carrier system and one or more emollients. Lotions typically comprise from about 1% to about 20%, preferably from about 5% to about 10%, of emollient; from about 50% to about 90%, preferably from about 60% to about 80%, water; and farnesol in the above described amounts. A cream typically comprises from about 5% to about 50%, preferably from about 10% to about 20%, of emollient; from about 45% to about 85%, preferably from about 50% to about 75%, water; and the farnesol in the above described amounts.

Ointments of the present invention may comprise a simple carrier base of animal or vegetable oils or semi-solid hydrocarbons (oleaginous); absorption ointment bases which absorb water to form emulsions; or water soluble carriers, e.g., a water soluble solution carrier. Ointments may further comprise a thickening agent, such as described in Sagarin, *Cosmetics, Science and Technology*, 2nd Edition, Vol. 1, pp. 72-73 (1972), incorporated herein by reference, and/or an emollient. For example, an ointment may comprise from about 2% to about 10% of an emollient; from about 0.1% to about 2% of a thickening agent; and farnesol in the above described amount.

Compositions of this invention useful for cleansing ("cleansers") are formulated with a suitable carrier, e.g., as described above, and preferably contain, in addition to the oxime compound in the above described amounts, from about 1% to about 90%, more preferably from about 5% to about 10%, of a dermatologically acceptable surfactant. The surfactant is suitably selected from anionic, nonionic, zwitterionic, amphoteric and ampholytic surfactants, as well as mixtures of these surfactants. Such surfactants are well known to those skilled in the detergency art. Nonlimiting examples of possible surfactants include isoceteth-20, sodium methyl cocoyl taurate, sodium methyl oleoyl taurate, and sodium lauryl sulfate. See U.S. Patent No. 4,800,197, to Kowcz et al., issued January 24, 1989, which is incorporated herein by reference in its entirety, for exemplary surfactants useful herein. Examples of a broad variety of additional surfactants useful herein are described in McCutcheon's *Detergents and Emulsifiers*, North American Edition (1986), published by Allured Publishing Corporation. The cleansing compositions can optionally contain, at their art-established levels, other materials which are conventionally used in cleansing compositions.

The physical form of the cleansing compositions is not critical. The compositions can be, for example, formulated as toilet bars, liquids, shampoos, bath gels, hair conditioners, hair tonics, pastes, or mousses. Toilet bars are most preferred since this is the form of cleansing agent most commonly used to wash the skin. Rinse-off cleansing compositions, such as shampoos, require a delivery system adequate to deposit sufficient levels of actives on the skin and scalp. A preferred delivery system involves the use of insoluble complexes. For a more complete disclosure of such delivery systems, see U.S. Patent 4,835,148, Barford et al., issued May 30, 1989.

As used herein, the term "foundation" refers to a liquid, semi-liquid, semi-solid, or solid skin cosmetic which includes, but is not limited to lotions, creams, gels, pastes, cakes, and the like. Typically the foundation is used over a large area of the skin, such as over the face, to provide a particular look. Foundations are typically used to provide an adherent base for color cosmetics such as rouge, blusher, powder and the like, and tend to hide skin imperfections and impart a smooth, even appearance to the skin. Foundations of the present invention include a dermatologically acceptable carrier for the farnesol and may include conventional ingredients such as oils, colorants, pigments, emollients, fragrances, waxes, stabilizers, and the like. Exemplary carriers and such other ingredients which are suitable for use herein are described, for example, in copending patent application Serial No. 08/430,961, filed on April 28, 1995 in the names of Marcia L. Canter, Brian D. Barford, and Brian D. Hofrichter, and U.K. Patent Application GB 2274585-A, published on Jan. 23, 1993.

Optional Components

The compositions of the present invention may contain a variety of other ingredients such as are conventionally used in a given product type provided that they do not unacceptably alter the benefits of the invention.

In a preferred embodiment, where the composition is to be in contact with mammalian keratinous tissue, the optional components should be suitable for application to mammalian keratinous tissue, that is, when incorporated into the composition they are suitable for use in contact with mammalian keratinous tissue, especially that of humans, without undue toxicity, incompatibility, instability, allergic response, and the like within the scope of sound medical judgment. The CTFA Cosmetic Ingredient Handbook, Second Edition (1992) describes a wide variety of nonlimiting cosmetic and pharmaceutical ingredients commonly used in the skin care industry, which are suitable for use in the compositions of the present invention. Examples of these ingredient classes include: abrasives, absorbents, aesthetic components such as fragrances, pigments, colorings/colorants, essential oils, skin sensates, astringents, etc. (e.g., clove oil, menthol, camphor, eucalyptus oil, eugenol, menthyl lactate, witch hazel distillate), anti-acne agents, anti-caking agents, antifoaming agents, antimicrobial agents (e.g., iodopropyl butylcarbamate), antioxidants, binders, biological additives, buffering agents, bulking agents, chelating agents, chemical additives, colorants, cosmetic astringents, cosmetic biocides, denaturants, drug astringents, external analgesics, film formers or materials, e.g., polymers, for aiding the film-forming properties and substantivity of the composition (e.g., copolymer of eicosene and vinyl pyrrolidone), opacifying agents, pH adjusters,

propellants, reducing agents, sequestrants, skin bleaching and lightening agents (e.g., hydroquinone, kojic acid, ascorbic acid, magnesium ascorbyl phosphate, ascorbyl glucosamine), skin-conditioning agents (e.g., humectants, including miscellaneous and occlusive), skin soothing and/or healing agents (e.g., panthenol and derivatives (e.g., ethyl panthenol), aloe vera, pantothenic acid and its derivatives, allantoin, bisabolol, and dipotassium glycyrrhizinate), skin treating agents, thickeners, and vitamins and derivatives thereof.

In any embodiment of the present invention, however, the actives useful herein can be categorized by the benefit they provide or by their postulated mode of action. However, it is to be understood that the actives useful herein can in some instances provide more than one benefit or operate via more than one mode of action. Therefore, classifications herein are made for the sake of convenience and are not intended to limit the active to that particular application or applications listed.

Desquamation Actives

A safe and effective amount of a desquamation active may be added to the compositions of the present invention, more preferably from about 0.1% to about 10%, even more preferably from about 0.2% to about 5%, also preferably from about 0.5% to about 4%, by weight of the composition. Desquamation actives enhance the skin appearance benefits of the present invention. For example, the desquamation actives tend to improve the texture of the skin (e.g., smoothness). One desquamation system that is suitable for use herein comprises sulfhydryl compounds and zwitterionic surfactants and is described in copending application Serial No. 08/480,632, filed on June 7, 1995 in the name of Donald L. Bissett, corresponding to PCT Application No. U.S. 95/08136, filed 6/29/95. Another desquamation system that is suitable for use herein comprises salicylic acid and zwitterionic surfactants and is described in copending patent application Serial No. 08/554,944, filed on November 13, 1995 as a continuation of Serial No. 08/209,401, filed on March 9, 1994 in the name of Bissett, corresponding to PCT Application No. 94/12745, filed 11/4/94, published 5/18/95. Zwitterionic surfactants such as described in these applications are also useful as desquamatory agents herein, with cetyl betaine being particularly preferred.

Anti-Acne Actives

The compositions of the present invention may comprise a safe and effective amount of one or more anti-acne actives. Examples of useful anti-acne actives include resorcinol, sulfur, salicylic acid, erythromycin, zinc, etc. Further examples of suitable anti-acne actives are described in further detail in U. S. Patent No. 5,607,980, issued to McAtee et al, on March 4, 1997.

Anti-Wrinkle Actives/Anti-Atrophy Actives

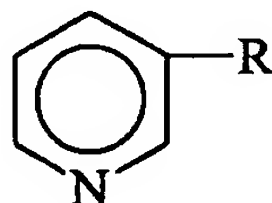
The compositions of the present invention may further comprise a safe and effective amount of one or more anti-wrinkle actives or anti-atrophy actives. Exemplary anti-wrinkle/anti-atrophy actives suitable for use in the compositions of the present invention include sulfur-containing D and L amino acids and their derivatives and salts, particularly the N-acetyl derivatives, a preferred example of which is N-acetyl-L-cysteine; thiols, e.g. ethane thiol; hydroxy acids (e.g., glycolic acid, lactic acid, and the like), phytic acid, lipoic acid; lysophosphatidic acid, skin peel agents (e.g., phenol and the like), vitamin B3 compounds and

retinoids which enhance the keratinous tissue appearance benefits of the present invention, especially in regulating keratinous tissue condition, e.g., skin condition.

a) Vitamin B3 Compounds

The compositions of the present invention may comprise a safe and effective amount of a vitamin B3 compound. Vitamin B3 compounds are particularly useful for regulating skin condition as described in co-pending U. S. Application Serial No. 08/834,010, filed April 11, 1997 (corresponding to international publication WO 97/39733 A1, published October 30, 1997). When vitamin B3 compounds are present in the compositions of the instant invention, the compositions preferably comprise from about 0.01% to about 50%, more preferably from about 0.1% to about 10%, even more preferably from about 0.5% to about 10%, and still more preferably from about 1% to about 5%, most preferably from about 2% to about 5%, by weight of the composition, of the vitamin B3 compound.

As used herein, "vitamin B3 compound" means a compound having the formula:



wherein R is - CONH₂ (i.e., niacinamide), - COOH (i.e., nicotinic acid) or - CH₂OH (i.e., nicotiny alcohol); derivatives thereof; and salts of any of the foregoing.

Exemplary derivatives of the foregoing vitamin B3 compounds include nicotinic acid esters, including non-vasodilating esters of nicotinic acid (e.g., tocopheryl nicotinate), nicotiny amino acids, nicotiny alcohol esters of carboxylic acids, nicotinic acid N-oxide and niacinamide N-oxide.

Examples of suitable vitamin B3 compounds are well known in the art and are commercially available from a number of sources, e.g., the Sigma Chemical Company (St. Louis, MO); ICN Biomedicals, Inc. (Irvin, CA) and Aldrich Chemical Company (Milwaukee, WI).

The vitamin compounds may be included as the substantially pure material, or as an extract obtained by suitable physical and/or chemical isolation from natural (e.g., plant) sources.

Preferred vitamin B3 compounds are niacinamide, tocopherol nicotinate, and mixtures thereof.

b) Retinoids

The compositions of the present invention may also comprise a retinoid. As used herein, "retinoid" includes all natural and/or synthetic analogs of Vitamin A or retinol-like compounds which possess the biological activity of Vitamin A in the skin as well as the geometric isomers and stereoisomers of these compounds. The retinoid is preferably retinol, retinol esters (e.g., C₂ - C₂₂ alkyl esters of retinol, including retinyl palmitate, retinyl acetate, retinyl propionate), retinal, and/or retinoic acid (including all-trans retinoic acid and/or 13-cis-retinoic acid), more preferably retinoids other than retinoic acid. These compounds are well known in the art and are commercially available from a number of sources, e.g., Sigma Chemical Company (St. Louis, MO), and Boehringer Mannheim (Indianapolis, IN). Other retinoids which are useful herein are described in U.S. Patent Nos. 4,677,120, issued Jun. 30, 1987 to Parish et al.; 4,885,311, issued

Dec. 5, 1989 to Parish et al.; 5,049,584, issued Sep. 17, 1991 to Purcell et al.; 5,124,356, issued Jun. 23, 1992 to Purcell et al.; and Reissue 34,075, issued Sep. 22, 1992 to Purcell et al.. Other suitable retinoids are tocopheryl-retinoate [tocopherol ester of retinoic acid (trans- or cis-), adapalene {6-[3-(1-adamantyl)-4-methoxyphenyl]-2-naphthoic acid}, and tazarotene (ethyl 6-[2-(4,4-dimethylthiochroman-6-yl)-ethynyl]nicotinate). Preferred retinoids are retinol, retinyl palmitate, retinyl acetate, retinyl propionate, retinal and combinations thereof.

The retinoid may be included as the substantially pure material, or as an extract obtained by suitable physical and/or chemical isolation from natural (e.g., plant) sources. The retinoid is preferably substantially pure, more preferably essentially pure.

The compositions of this invention may contain a safe and effective amount of the retinoid, such that the resultant composition is safe and effective for regulating keratinous tissue condition, preferably for regulating visible and/or tactile discontinuities in skin, more preferably for regulating signs of skin aging, even more preferably for regulating visible and/or tactile discontinuities in skin texture associated with skin aging. The compositions preferably contain from or about 0.005% to or about 2%, more preferably 0.01% to or about 2%, retinoid. Retinol is most preferably used in an amount of from or about 0.01% to or about 0.15%; retinol esters are most preferably used in an amount of from or about 0.01% to or about 2% (e.g., about 1%); retinoic acids are most preferably used in an amount of from or about 0.01% to or about 0.25%; tocopheryl-retinoate, adapalene, and tazarotene are most preferably used in an amount of from or about 0.01% to or about 2%.

Where the compositions of the present invention contain both a retinoid and a Vitamin B3 compound, the retinoid is preferably used in the above amounts, and the vitamin B3 compound is preferably used in an amount of from or about 0.1% to or about 10%, more preferably from or about 2% to or about 5%.

Anti-Oxidants/Radical Scavengers

The compositions of the present invention may include a safe and effective amount of an anti-oxidant/radical scavenger. The anti-oxidant/radical scavenger is especially useful for providing protection against UV radiation which can cause increased scaling or texture changes in the stratum corneum and against other environmental agents which can cause skin damage.

A safe and effective amount of an anti-oxidant/radical scavenger may be added to the compositions of the subject invention, preferably from about 0.1% to about 10%, more preferably from about 1% to about 5%, of the composition.

Anti-oxidants/radical scavengers such as ascorbic acid (vitamin C) and its salts, ascorbyl esters of fatty acids, ascorbic acid derivatives (e.g., magnesium ascorbyl phosphate), tocopherol (vitamin E), tocopherol sorbate, tocopherol acetate, other esters of tocopherol, butylated hydroxy benzoic acids and their salts, 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid (commercially available under the tradename TroloxR), gallic acid and its alkyl esters, especially propyl gallate, uric acid and its salts and alkyl esters, sorbic acid and its salts, lipoic acid, amines (e.g., N,N-diethylhydroxylamine, amino-guanidine), sulfhydryl

compounds (e.g., glutathione), dihydroxy fumaric acid and its salts, lysine pidolate, arginine pilolate, nordihydroguaiaretic acid, bioflavonoids, lysine, methionine, proline, superoxide dismutase, silymarin, tea extracts, grape skin/seed extracts, melanin, and rosemary extracts may be used. Preferred antioxidants/radical scavengers are selected from tocopherol sorbate and other esters of tocopherol, more preferably tocopherol sorbate. For example, the use of tocopherol sorbate in topical compositions and applicable to the present invention is described in U.S. Patent No. 4,847,071, issued on July 11, 1989 to Donald L. Bissett, Rodney D. Bush and Ranjit Chatterjee.

Chelators

The compositions of the present invention may also comprise a safe and effective amount of a chelator or chelating agent. As used herein, "chelator" or "chelating agent" means an active agent capable of removing a metal ion from a system by forming a complex so that the metal ion cannot readily participate in or catalyze chemical reactions. The inclusion of a chelating agent is especially useful for providing protection against UV radiation which can contribute to excessive scaling or skin texture changes and against other environmental agents which can cause skin damage.

A safe and effective amount of a chelating agent may be added to the compositions of the subject invention, preferably from about 0.1% to about 10%, more preferably from about 1% to about 5%, of the composition. Exemplary chelators that are useful herein are disclosed in International Publication No. 91/16035, Bush et al., published 10/31/95; and International Publication No. 91/16034, Bush et al., published 10/31/95.

Flavonoids

The compositions of the present invention may optionally comprise a flavonoid compound. Flavonoids are broadly disclosed in U.S. Patents 5,686,082 and 5,686,367, both of which are herein incorporated by reference. Flavonoids suitable for use in the present invention are flavanones selected from the group consisting of unsubstituted flavanones, mono-substituted flavanones, and mixtures thereof; chalcones selected from the group consisting of unsubstituted chalcones, mono-substituted chalcones, di-substituted chalcones, tri-substituted chalcones, and mixtures thereof; flavones selected from the group consisting of unsubstituted flavones, mono-substituted flavones, di-substituted flavones, and mixtures thereof; one or more isoflavones; coumarins selected from the group consisting of unsubstituted coumarins, mono-substituted coumarins, di-substituted coumarins, and mixtures thereof; chromones selected from the group consisting of unsubstituted chromones, mono-substituted chromones, di-substituted chromones, and mixtures thereof; one or more dicoumarols; one or more chromanones; one or more chromanols; isomers (e.g., cis/trans isomers) thereof; and mixtures thereof. By the term "substituted" as used herein means flavonoids wherein one or more hydrogen atom of the flavonoid has been independently replaced with hydroxyl, C1-C8 alkyl, C1-C4 alkoxy, O-glycoside, and the like or a mixture of these substituents.

Examples of suitable flavonoids include, but are not limited to, unsubstituted flavonone, mono-hydroxy flavanones (e.g., 2'-hydroxy flavanone, 6-hydroxy flavanone, 7-hydroxy flavanone, etc.), mono-alkoxy flavanones (e.g., 5-methoxy flavanone, 6-methoxy flavanone, 7-methoxy flavanone, 4'-methoxy

flavanone, etc.), unsubstituted chalcone (especially unsubstituted trans-chalcone), mono-hydroxy chalcones (e.g., 2'-hydroxy chalcone, 4'-hydroxy chalcone, etc.), di-hydroxy chalcones (e.g., 2',4'-dihydroxy chalcone, 2',4'-dihydroxy chalcone, 2,2'-dihydroxy chalcone, 2',3'-dihydroxy chalcone, 2',5'-dihydroxy chalcone, etc.), and tri-hydroxy chalcones (e.g., 2',3',4'-trihydroxy chalcone, 4,2',4'-trihydroxy chalcone, 2,2',4'-trihydroxy chalcone, etc.), unsubstituted flavone, 7,2'-dihydroxy flavone, 3',4'-dihydroxy naphthoflavone, 4'-hydroxy flavone, 5,6-benzoflavone, and 7,8-benzoflavone, unsubstituted isoflavone, daidzein (7,4'-dihydroxy isoflavone), 5,7-dihydroxy-4'-methoxy isoflavone, soy isoflavones (a mixture extracted from soy), unsubstituted coumarin, 4-hydroxy coumarin, 7-hydroxy coumarin, 6-hydroxy-4-methyl coumarin, unsubstituted chromone, 3-formyl chromone, 3-formyl-6-isopropyl chromone, unsubstituted dicoumarol, unsubstituted chromanone, unsubstituted chromanol, and mixtures thereof.

Preferred for use herein are unsubstituted flavanone, methoxy flavanones, unsubstituted chalcone, 2',4'-dihydroxy chalcone, and mixtures thereof. Most preferred are unsubstituted flavanone, unsubstituted chalcone (especially the trans isomer), and mixtures thereof.

They can be synthetic materials or obtained as extracts from natural sources (e.g., plants). The naturally sourced material can also further be derivatized (e.g., an ester or ether derivative prepared following extraction from a natural source). Flavonoid compounds useful herein are commercially available from a number of sources, e.g., Indofine Chemical Company, Inc. (Somerville, New Jersey), Steraloids, Inc. (Wilton, New Hampshire), and Aldrich Chemical Company, Inc. (Milwaukee, Wisconsin).

Mixtures of the above flavonoid compounds may also be used.

The herein described flavonoid compounds are preferably present in the instant invention at concentrations of from about 0.01% to about 20%, more preferably from about 0.1% to about 10% , and most preferably from about 0.5% to about 5%.

Anti-Inflammatory Agents

A safe and effective amount of an anti-inflammatory agent may be added to the compositions of the present invention, preferably from about 0.1% to about 10%, more preferably from about 0.5% to about 5%, of the composition. The anti-inflammatory agent enhances the skin appearance benefits of the present invention, e.g., such agents contribute to a more uniform and acceptable skin tone or color. The exact amount of anti-inflammatory agent to be used in the compositions will depend on the particular anti-inflammatory agent utilized since such agents vary widely in potency.

Steroidal anti-inflammatory agents, including but not limited to, corticosteroids such as hydrocortisone, hydroxyltriamcinolone, alpha-methyl dexamethasone, dexamethasone-phosphate, beclomethasone dipropionates, clobetasol valerate, desonide, desoxymethasone, desoxycorticosterone acetate, dexamethasone, dichlorisone, diflorasone diacetate, diflucortolone valerate, fludrenolone, flucorolone acetonide, fludrocortisone, flumethasone pivalate, fluosinolone acetonide, fluocinonide, flucortine butylesters, fluocortolone, fluprednidene (fluprednylidene) acetate, flurandrenolone, halcinonide, hydrocortisone acetate, hydrocortisone butyrate, methylprednisolone, triamcinolone acetonide, cortisone, cortodoxone, flucetonide, fludrocortisone, difluorosone diacetate, fluradrenolone, fludrocortisone,

diffurosone diacetate, fluradrenolone acetonide, medrysone, amcinafel, amcinafide, betamethasone and the balance of its esters, chloroprednisone, chlorprednisone acetate, clocortelone, clescinolone, dichlorisone, diflurprednate, flucoronide, flunisolide, fluoromethalone, fluperolone, fluprednisolone, hydrocortisone valerate, hydrocortisone cyclopentylpropionate, hydrocortamate, meprednisone, paramethasone, prednisolone, prednisone, beclomethasone dipropionate, triamcinolone, and mixtures thereof may be used. The preferred steroidal anti-inflammatory for use is hydrocortisone.

A second class of anti-inflammatory agents which is useful in the compositions includes the nonsteroidal anti-inflammatory agents. The variety of compounds encompassed by this group are well-known to those skilled in the art. For detailed disclosure of the chemical structure, synthesis, side effects, etc. of non-steroidal anti-inflammatory agents, one may refer to standard texts, including *Anti-inflammatory and Anti-Rheumatic Drugs*, K. D. Rainsford, Vol. I-III, CRC Press, Boca Raton, (1985), and *Anti-inflammatory Agents, Chemistry and Pharmacology*, 1, R. A. Scherrer, et al., Academic Press, New York (1974).

Specific non-steroidal anti-inflammatory agents useful in the composition invention include, but are not limited to:

- 1) the oxicams, such as piroxicam, isoxicam, tenoxicam, sudoxicam, and CP-14,304;
- 2) the salicylates, such as aspirin, disalcid, benorylate, trilisate, safapryn, solprin, diflunisal, and fendosal;
- 3) the acetic acid derivatives, such as diclofenac, fenclofenac, indomethacin, sulindac, tolmetin, isoxepac, furofenac, tiopinac, zidometacin, acematacin, fentiazac, zomepirac, clindanac, oxepinac, felbinac, and ketorolac;
- 4) the fenamates, such as mefenamic, meclofenamic, flufenamic, niflumic, and tolfenamic acids;
- 5) the propionic acid derivatives, such as ibuprofen, naproxen, benoxaprofen, flurbiprofen, ketoprofen, fenoprofen, fenbufen, indoprofen, pirprofen, carprofen, oxaprozin, pranoprofen, miroprofen, tioxaprofen, suprofen, alminoprofen, and tiaprofenic; and
- 6) the pyrazoles, such as phenylbutazone, oxyphenbutazone, feprazone, azapropazone, and trimethazone.

Mixtures of these non-steroidal anti-inflammatory agents may also be employed, as well as the dermatologically acceptable salts and esters of these agents. For example, etofenamate, a flufenamic acid derivative, is particularly useful for topical application. Of the nonsteroidal anti-inflammatory agents, ibuprofen, naproxen, flufenamic acid, etofenamate, aspirin, mefenamic acid, meclofenamic acid, piroxicam and felbinac are preferred; ibuprofen, naproxen, ketoprofen, etofenamate, aspirin and flufenamic acid are most preferred.

Finally, so-called "natural" anti-inflammatory agents are useful in methods of the present invention. Such agents may suitably be obtained as an extract by suitable physical and/or chemical isolation from natural sources (e.g., plants, fungi, by-products of microorganisms). For example, candelilla wax, alpha

bisabolol, aloe vera, Manjistha (extracted from plants in the genus *Rubia*, particularly *Rubia Cordifolia*), and Guggal (extracted from plants in the genus *Commiphora*, particularly *Commiphora Mukul*), kola extract, chamomile, and sea whip extract, may be used.

Additional anti-inflammatory agents useful herein include compounds of the Licorice (the plant genus/species *Glycyrrhiza glabra*) family, including glycyrrhetic acid, glycyrrhizic acid, and derivatives thereof (e.g., salts and esters). Suitable salts of the foregoing compounds include metal and ammonium salts. Suitable esters include C2 - C24 saturated or unsaturated esters of the acids, preferably C10 - C24, more preferably C16 - C24. Specific examples of the foregoing include oil soluble licorice extract, the glycyrrhizic and glycyrrhetic acids themselves, monoammonium glycyrrhizinate, monopotassium glycyrrhizinate, dipotassium glycyrrhizinate, 1-beta-glycyrrhetic acid, stearyl glycyrrhetinate, and 3-stearyloxy-glycyrrhetinic acid, and disodium 3-succinyloxy-beta-glycyrrhetinate. Stearyl glycyrrhetinate is preferred.

Anti-Cellulite Agents

The compositions of the present invention may also comprise a safe and effective amount of an anti-cellulite agent. Suitable agents may include, but are not limited to, xanthine compounds (e.g., caffeine, theophylline, theobromine, and aminophylline).

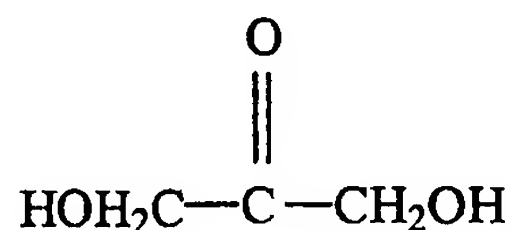
Topical Anesthetics

The compositions of the present invention may also comprise a safe and effective amount of a topical anesthetic. Examples of topical anesthetic drugs include benzocaine, lidocaine, bupivacaine, chlorprocaine, dibucaine, etidocaine, mepivacaine, tetracaine, dyclonine, hexylcaine, procaine, cocaine, ketamine, pramoxine, phenol, and pharmaceutically acceptable salts thereof.

Tanning Actives

The compositions of the present invention may comprise a tanning active. When present, it is preferable that the compositions comprise from about 0.1% to about 20%, more preferably from about 2% to about 7%, and most preferably from about 3% to about 6%, by weight of the composition, of dihydroxyacetone as an artificial tanning active.

Dihydroxyacetone, which is also known as DHA or 1,3-dihydroxy-2-propanone, is a white to off-white, crystalline powder. This material can be represented by the chemical formula C₃H₆O₃ and the following chemical structure.



The compound can exist as a mixture of monomers and dimers, with the dimers predominating in the solid crystalline state. Upon heating or melting, the dimers break down to yield the monomers. This conversion of the dimeric form to the monomeric form also occurs in aqueous solution. Dihydroxyacetone is also known to be more stable at acidic pH values. See *The Merck Index*, Tenth Edition, entry 3167, p. 463

(1983), and "Dihydroxyacetone for Cosmetics", E. Merck Technical Bulletin, 03-304 110, 319 897, 180 588.

Skin Lightening Agents

The compositions of the present invention may comprise an additional skin lightening agent. When used, the compositions preferably comprise from about 0.1% to about 10%, more preferably from about 0.2% to about 5%, also preferably from about 0.5% to about 2%, by weight of the composition, of a skin lightening agent. Suitable skin lightening agents include those known in the art, including kojic acid, arbutin, niacinamide, ascorbic acid and derivatives thereof, e.g., magnesium ascorbyl phosphate or sodium ascorbyl phosphate. Skin lightening agents suitable for use herein also include those described in copending patent application Serial No. 08/479,935, filed on June 7, 1995 in the name of Hillebrand, corresponding to PCT Application No. U.S. 95/07432, filed 6/12/95; and copending patent application Serial No. 08/390,152, filed on February 24, 1995 in the names of Kalla L. Kvalnes, Mitchell A. DeLong, Barton J. Bradbury, Curtis B. Motley, and John D. Carter, corresponding to PCT Application No. U.S. 95/02809, filed 3/1/95, published 9/8/95.

Antimicrobial and Antifungal Actives

The compositions of the present invention may comprise an antimicrobial or antifungal active. Such actives are capable of destroying microbes, preventing the development of microbes or preventing the pathogenic action of microbes. A safe and effective amount of an antimicrobial or antifungal active may be added to the present compositions, preferably, from about 0.001% to about 10%, more preferably from about 0.01% to about 5%, and most preferably from about 0.05% to about 2%.

Examples of antimicrobial and antifungal actives include β -lactam drugs, quinolone drugs, ciprofloxacin, norfloxacin, tetracycline, erythromycin, amikacin, 2,4,4'-trichloro-2'-hydroxy diphenyl ether, 3,4,4'-trichlorobanilide, phenoxyethanol, phenoxy propanol, phenoxyisopropanol, doxycycline, capreomycin, chlorhexidine, chlortetracycline, oxytetracycline, clindamycin, ethambutol, hexamidine isethionate, metronidazole, pentamidine, gentamicin, kanamycin, lineomycin, methacycline, methenamine, minocycline, neomycin, netilmicin, paromomycin, streptomycin, tobramycin, miconazole, tetracycline hydrochloride, erythromycin, zinc erythromycin, erythromycin estolate, erythromycin stearate, amikacin sulfate, doxycycline hydrochloride, capreomycin sulfate, chlorhexidine gluconate, chlorhexidine hydrochloride, chlortetracycline hydrochloride, oxytetracycline hydrochloride, clindamycin hydrochloride, ethambutol hydrochloride, metronidazole hydrochloride, pentamidine hydrochloride, gentamicin sulfate, kanamycin sulfate, lineomycin hydrochloride, methacycline hydrochloride, methenamine hippurate, methenamine mandelate, minocycline hydrochloride, neomycin sulfate, netilmicin sulfate, paromomycin sulfate, streptomycin sulfate, tobramycin sulfate, miconazole hydrochloride, ketoconazole, amantadine hydrochloride, amantadine sulfate, octopirox, parachlorometa xlenol, nystatin, tolnaftate, zinc pyrithione and clotrimazole.

Preferred examples of actives useful herein include those selected from the group consisting of salicylic acid, benzoyl peroxide, 3-hydroxy benzoic acid, glycolic acid, lactic acid, 4-hydroxy benzoic acid,

acetyl salicylic acid, 2-hydroxybutanoic acid, 2-hydroxypentanoic acid, 2-hydroxyhexanoic acid, cis-retinoic acid, trans-retinoic acid, retinol, phytic acid, N-acetyl-L-cysteine, lipoic acid, azelaic acid, arachidonic acid, benzoylperoxide, tetracycline, ibuprofen, naproxen, hydrocortisone, acetaminophen, resorcinol, phenoxyethanol, phenoxypropanol, phenoxyisopropanol, 2,4,4'-trichloro-2'-hydroxy diphenyl ether, 3,4,4'-trichlorocarbanilide, octopirox, lidocaine hydrochloride, clotrimazole, miconazole, ketoconazole, neocycin sulfate, and mixtures thereof.

Sunscreen Actives

Exposure to ultraviolet light can result in excessive scaling and texture changes of the stratum corneum. Therefore, the compositions of the subject invention may optionally contain a sunscreen active. As used herein, "sunscreen active" includes both sunscreen agents and physical sunblocks. Suitable sunscreen actives may be organic or inorganic.

A wide variety of conventional sunscreen actives are suitable for use herein. Sagarin, et al., at Chapter VIII, pages 189 et seq., of *Cosmetics Science and Technology* (1972), discloses numerous suitable actives. Specific suitable sunscreen actives include, for example: p-aminobenzoic acid, its salts and its derivatives (ethyl, isobutyl, glyceryl esters; p-dimethylaminobenzoic acid); anthranilates (i.e., o-amino-benzoates; methyl, menthyl, phenyl, benzyl, phenylethyl, linalyl, terpinyl, and cyclohexenyl esters); salicylates (amyl, phenyl, octyl, benzyl, menthyl, glyceryl, and di-pro-pyleneglycol esters); cinnamic acid derivatives (menthyl and benzyl esters, a-phenyl cinnamitrile; butyl cinnamoyl pyruvate); dihydroxycinnamic acid derivatives (umbelliferone, methylumbelliferone, methylaceto-umbelliferone); trihydroxy-cinnamic acid derivatives (esculetin, methylesculetin, daphnetin, and the glucosides, esculin and daphnin); hydrocarbons (diphenylbutadiene, stilbene); dibenzalacetone and benzalacetophenone; naphtholsulfonates (sodium salts of 2-naphthol-3,6-disulfonic and of 2-naphthol-6,8-disulfonic acids); dihydroxynaphthoic acid and its salts; o- and p-hydroxybiphenyldisulfonates; coumarin derivatives (7-hydroxy, 7-methyl, 3-phenyl); diazoles (2-acetyl-3-bromoindazole, phenyl benzoxazole, methyl naphthoxazole, various aryl benzothiazoles); quinine salts (bisulfate, sulfate, chloride, oleate, and tannate); quinoline derivatives (8-hydroxyquinoline salts, 2-phenylquinoline); hydroxy- or methoxy-substituted benzophenones; uric and violuric acids; tannic acid and its derivatives (e.g., hexaethylether); (butyl carboto) (6-propyl piperonyl) ether; hydroquinone; benzophenones (oxybenzene, sulisobenzene, dioxybenzene, benzo-resorcinol, 2,2',4,4'-tetrahydroxybenzophenone, 2,2'-dihydroxy-4,4'-dimethoxybenzophenone, octabenzene; 4-isopropyl-dibenzoylmethane; butylmethoxydibenzoylmethane; etocrylene; octocrylene; [3-(4'-methylbenzylidene bornan-2-one) and 4-isopropyl-di-benzoylmethane.

Of these, 2-ethylhexyl-p-methoxycinnamate (commercially available as PARSOL MCX), 4,4'-t-butyl methoxydibenzoyl-methane (commercially available as PARSOL 1789), 2-hydroxy-4-methoxybenzophenone, octyldimethyl-p-aminobenzoic acid, digalloyltriolate, 2,2-dihydroxy-4-methoxybenzophenone, ethyl-4-(bis(hydroxy-propyl))aminobenzoate, 2-ethylhexyl-2-cyano-3,3-diphenylacrylate, 2-ethylhexyl-salicylate, glyceryl-p-aminobenzoate, 3,3,5-tri-methylcyclohexylsalicylate, methylanthranilate, p-dimethyl-aminobenzoic acid or aminobenzoate, 2-ethylhexyl-p-dimethyl-amino-

benzoate, 2-phenylbenzimidazole-5-sulfonic acid, 2-(p-dimethylaminophenyl)-5-sulfonicbenzoxazoic acid, octocrylene and mixtures of these compounds, are preferred.

More preferred organic sunscreen actives useful in the compositions useful in the subject invention are 2-ethylhexyl-p-methoxycinnamate, butylmethoxydibenzoyl-methane, 2-hydroxy-4-methoxybenzophenone, 2-phenylbenzimidazole-5-sulfonic acid, octyldimethyl-p-aminobenzoic acid, octocrylene and mixtures thereof.

Also particularly useful in the compositions are sunscreen actives such as those disclosed in U.S. Patent No. 4,937,370 issued to Sabatelli on June 26, 1990, and U.S. Patent No. 4,999,186 issued to Sabatelli & Spirnak on March 12, 1991. The sunscreens disclosed therein have, in a single molecule, two distinct chromophore moieties which exhibit different ultra-violet radiation absorption spectra. One of the chromophore moieties absorbs predominantly in the UVB radiation range and the other absorbs strongly in the UVA radiation range.

Preferred members of this class of sunscreens are 4-N,N-(2-ethylhexyl)methylaminobenzoic acid ester of 2,4-dihydroxybenzophenone; N,N-di-(2-ethylhexyl)-4-aminobenzoic acid ester with 4-hydroxydibenzoylmethane; 4-N,N-(2-ethylhexyl)methylaminobenzoic acid ester with 4-hydroxydibenzoylmethane; 4-N,N-(2-ethylhexyl)methylaminobenzoic acid ester of 2-hydroxy-4-(2-hydroxyethoxy)benzophenone; 4-N,N-(2-ethylhexyl)-methylaminobenzoic acid ester of 4-(2-hydroxyethoxy)dibenzoylmethane; N,N-di-(2-ethylhexyl)-4-aminobenzoic acid ester of 2-hydroxy-4-(2-hydroxyethoxy)benzophenone; and N,N-di-(2-ethylhexyl)-4-aminobenzoic acid ester of 4-(2-hydroxyethoxy)dibenzoylmethane, zinc oxide, titanium oxide, and mixtures thereof.

Especially preferred sunscreen actives include 4,4'-t-butylmethoxydibenzoylmethane, 2-ethylhexyl-p-methoxycinnamate, phenyl benzimidazole sulfonic acid, zinc oxide, titanium dioxide, octocrylene, and combinations thereof.

A safe and effective amount of the sunscreen active is used, typically from about 1% to about 20%, more typically from about 2% to about 10% by weight of the composition. Exact amounts will vary depending upon the sunscreen chosen and the desired Sun Protection Factor (SPF).

Conditioning Agents

The compositions of the present invention may comprise a conditioning agent selected from the group consisting of humectants, moisturizers, or skin conditioners. A variety of these materials can be employed and each can be present at a level of from about 0.01% to about 20%, more preferably from about 0.1% to about 10%, and most preferably from about 0.5% to about 7% by weight of the composition. These materials include, but are not limited to, guanidine; urea; glycolic acid and glycolate salts (e.g. ammonium and quaternary alkyl ammonium); salicylic acid; lactic acid and lactate salts (e.g., ammonium and quaternary alkyl ammonium); aloe vera in any of its variety of forms (e.g., aloe vera gel); polyhydroxy alcohols such as sorbitol, glycerol, hexanetriol, butanetriol, propylene glycol, butylene glycol, hexylene glycol and the like; polyethylene glycols; sugars (e.g., melibiose) and starches; sugar and starch derivatives (e.g., alkoxyated glucose, fucose); hyaluronic acid; lactamide monoethanolamine; acetamide monoethanolamine; and

mixtures thereof. Also useful herein are the propoxylated glycerols described in U. S. Patent No. 4,976,953, to Orr et al, issued December 11, 1990.

Also useful are various C1-C30 monoesters and polyesters of sugars and related materials. These esters are derived from a sugar or polyol moiety and one or more carboxylic acid moieties. Such ester materials are further described in, U. S. Patent No. 2,831,854, U. S. Patent No. 4,005,196, to Jandacek, issued January 25, 1977; U. S. Patent No. 4,005,195, to Jandacek, issued January 25, 1977, U. S. Patent No. 5,306,516, to Letton et al, issued April 26, 1994; U. S. Patent No. 5,306,515, to Letton et al, issued April 26, 1994; U. S. Patent No. 5,305,514, to Letton et al, issued April 26, 1994; U. S. Patent No. 4,797,300, to Jandacek et al, issued January 10, 1989; U. S. Patent No. 3,963,699, to Rizzi et al, issued June 15, 1976; U. S. Patent No. 4,518,772, to Volpenhein, issued May 21, 1985; and U. S. Patent No. 4,517,360, to Volpenhein, issued May 21, 1985.

Preferably, the conditioning agent is selected from the group consisting of glycerol, urea, guanidine, sucrose polyester, and combinations thereof.

Thickening Agent (including thickeners and gelling agents)

The compositions of the present invention can comprise one or more thickening agents, preferably from about 0.1% to about 5%, more preferably from about 0.1% to about 3%, and most preferably from about 0.25% to about 2%, by weight of the composition.

Nonlimiting classes of thickening agents include those selected from the group consisting of:

a) Carboxylic Acid Polymers

These polymers are crosslinked compounds containing one or more monomers derived from acrylic acid, substituted acrylic acids, and salts and esters of these acrylic acids and the substituted acrylic acids, wherein the crosslinking agent contains two or more carbon-carbon double bonds and is derived from a polyhydric alcohol. Polymers useful in the present invention are more fully described in U. S. Patent No. 5,087,445, to Haffey et al, issued February 11, 1992; U. S. Patent No. 4,509,949, to Huang et al, issued April 5, 1985; U. S. Patent No. 2,798,053, to Brown, issued July 2, 1957; and in CTFA International Cosmetic Ingredient Dictionary, Fourth Edition, 1991, pp. 12 and 80.

Examples of commercially available carboxylic acid polymers useful herein include the carbomers, which are homopolymers of acrylic acid crosslinked with allyl ethers of sucrose or pentaerytritol. The carbomers are available as the Carbopol® 900 series from B.F. Goodrich (e.g., Carbopol® 954). In addition, other suitable carboxylic acid polymeric agents include copolymers of C10-30 alkyl acrylates with one or more monomers of acrylic acid, methacrylic acid, or one of their short chain (i.e., C1-4 alcohol) esters, wherein the crosslinking agent is an allyl ether of sucrose or pentaerytritol. These copolymers are known as acrylates/C10-30 alkyl acrylate crosspolymers and are commercially available as Carbopol® 1342, Carbopol® 1382, Permulen TR-1, and Permulen TR-2, from B.F. Goodrich. In other words, examples of carboxylic acid polymer thickeners useful herein are those selected from the group consisting of carbomers, acrylates/C10-C30 alkyl acrylate crosspolymers, and mixtures thereof.

b) Crosslinked Polyacrylate Polymers

The compositions of the present invention can optionally comprise crosslinked polyacrylate polymers useful as thickeners or gelling agents including both cationic and nonionic polymers, with the cationics being generally preferred. Examples of useful crosslinked nonionic polyacrylate polymers and crosslinked cationic polyacrylate polymers are those described in U. S. Patent No. 5,100,660, to Hawe et al, issued March 31, 1992; U. S. Patent No. 4,849,484, to Heard, issued July 18, 1989; U. S. Patent No. 4,835,206, to Farrar et al, issued May 30, 1989; U.S. Patent No. 4,628,078 to Glover et al issued December 9, 1986; U.S. Patent No. 4,599,379 to Flesher et al issued July 8, 1986; and EP 228,868, to Farrar et al, published July 15, 1987.

c) Polyacrylamide Polymers

The compositions of the present invention can optionally comprise polyacrylamide polymers, especially nonionic polyacrylamide polymers including substituted branched or unbranched polymers. Most preferred among these polyacrylamide polymers is the nonionic polymer given the CTFA designation polyacrylamide and isoparaffin and laureth-7, available under the Tradename Sepigel 305 from Seppic Corporation (Fairfield, NJ).

Other polyacrylamide polymers useful herein include multi-block copolymers of acrylamides and substituted acrylamides with acrylic acids and substituted acrylic acids. Commercially available examples of these multi-block copolymers include Hypan SR150H, SS500V, SS500W, SSSA100H, from Lipo Chemicals, Inc., (Patterson, NJ).

d) Polysaccharides

A wide variety of polysaccharides are useful herein. "Polysaccharides" refer to gelling agents which contain a backbone of repeating sugar (i.e., carbohydrate) units. Nonlimiting examples of polysaccharide gelling agents include those selected from the group consisting of cellulose, carboxymethyl hydroxyethylcellulose, cellulose acetate propionate carboxylate, hydroxyethylcellulose, hydroxyethyl ethylcellulose, hydroxypropylcellulose, hydroxypropyl methylcellulose, methyl hydroxyethylcellulose, microcrystalline cellulose, sodium cellulose sulfate, and mixtures thereof. Also useful herein are the alkyl substituted celluloses. In these polymers, the hydroxy groups of the cellulose polymer is hydroxyalkylated (preferably hydroxyethylated or hydroxypropylated) to form a hydroxyalkylated cellulose which is then further modified with a C10-C30 straight chain or branched chain alkyl group through an ether linkage. Typically these polymers are ethers of C10-C30 straight or branched chain alcohols with hydroxyalkylcelluloses. Examples of alkyl groups useful herein include those selected from the group consisting of stearyl, isostearyl, lauryl, myristyl, cetyl, isocetyl, cocoyl (i.e. alkyl groups derived from the alcohols of coconut oil), palmityl, oleyl, linoleyl, linolenyl, ricinoleyl, behenyl, and mixtures thereof. Preferred among the alkyl hydroxyalkyl cellulose ethers is the material given the CTFA designation cetyl hydroxyethylcellulose, which is the ether of cetyl alcohol and hydroxyethylcellulose. This material is sold under the tradename Natrosol® CS Plus from Aqualon Corporation (Wilmington, DE).

Other useful polysaccharides include scleroglucans comprising a linear chain of (1-3) linked glucose units with a (1-6) linked glucose every three units, a commercially available example of which is Clearogel™ CS11 from Michel Mercier Products Inc. (Mountainside, NJ).

e) Gums

Other thickening and gelling agents useful herein include materials which are primarily derived from natural sources. Nonlimiting examples of these gelling agent gums include materials selected from the group consisting of acacia, agar, algin, alginic acid, ammonium alginate, amylopectin, calcium alginate, calcium carrageenan, carnitine, carrageenan, dextrin, gelatin, gellan gum, guar gum, guar hydroxypropyltrimonium chloride, hectorite, hyaluronic acid, hydrated silica, hydroxypropyl chitosan, hydroxypropyl guar, karaya gum, kelp, locust bean gum, natto gum, potassium alginate, potassium carrageenan, propylene glycol alginate, sclerotium gum, sodium carboxymethyl dextran, sodium carrageenan, tragacanth gum, xanthan gum, and mixtures thereof.

Preferred compositions of the present invention include a thickening agent selected from the group consisting of carboxylic acid polymers, crosslinked polyacrylate polymers, polyacrylamide polymers, and mixtures thereof, more preferably selected from the group consisting of carboxylic acid polymers, polyacrylamide polymers, and mixtures thereof.

Preparation of Compositions

The compositions of the present invention are generally prepared by conventional methods such as are known in the art of making topical compositions. Such methods typically involve mixing of the ingredients in one or more steps to a relatively uniform state, with or without heating, cooling, application of vacuum, and the like.

Methods for Lightening Keratinous Tissue

The compositions of the present invention are useful for lightening keratinous tissue, preferably mammalian, and more preferably human keratinous tissue. In an even more preferred embodiment, the compositions of the present invention are useful for lightening human skin, more especially facial and hand skin. The compositions are especially useful for lightening hyperpigmented regions of skin. The methods discussed herein may also be used to lighten keratinous tissues such as hair, nails, etc..

The method of lightening keratinous tissue involves topically applying to the keratinous tissue in need of treatment a safe and effective amount of a composition comprising a safe and effective amount of an oxime compound and a dermatologically acceptable carrier for said oxime compound. The amount of the composition which is applied, the frequency of application and the period of use will vary widely depending upon the level of the oxime compound and/or other components of a given composition and the level of lightening desired, e.g., in light of the level of skin pigmentation present in the subject and the rate of further skin pigmentation.

In a preferred embodiment, the composition is chronically applied to mammalian skin, preferably human skin. By "chronic topical application" is meant substantially continuous topical application of the composition over an extended period during the subject's lifetime, preferably for a period of at least about

one week, more preferably for a period of at least about one month, even more preferably for at least about three months, even more preferably for at least about six months, and still more preferably for at least about one year. While benefits are obtainable after various maximum periods of use (e.g., two, five, ten or twenty years), it is preferred that chronic application continue throughout the subject's lifetime. Typically applications would be on the order of about once or twice per day over such extended periods, however application rates can vary, e.g., from about once per week up to about three times per day or more.

A wide range of quantities of the compositions of the present invention can be employed to provide a keratinous tissue lightening benefit. Quantities of the present compositions which are typically applied per application are from about 0.1 mg/cm² keratinous tissue to about 10 mg/cm² keratinous tissue. A particularly useful application amount is about 2 mg/cm² keratinous tissue.

The method of lightening keratinous tissue, especially skin, is preferably practiced by applying a composition in the form of a skin lotion, cream, gel, cosmetic (such as foundation), or the like which is intended to be left on the keratinous tissue for some esthetic, prophylactic, therapeutic or other benefit. After applying the composition to the keratinous tissue, it is preferably left on the keratinous tissue for a period of at least about 15 minutes, more preferably at least about 30 minutes, even more preferably at least about 1 hour, most preferably for at least several hours, e.g., up to about 12 hours. The composition can also be applied to keratinous tissue, e.g., skin, under a patch (occlusive, semi-occlusive, non-occlusive) or be contained in a patch which is then applied to the keratinous tissue. The patch can be left on the keratinous tissue for a brief period (e.g., approximately 5 minutes) or for an extended period (e.g., up to overnight).

Examples

The following examples further describe and demonstrate embodiments within the scope of the present invention. The examples are given solely for the purpose of illustration and are not to be construed as limitations of the present invention, as many variations thereof are possible without departing from the spirit and scope of the invention.

Example 1

A moisturizing lotion is prepared by combining the following components utilizing conventional mixing techniques.

Component	Weight Percent
Water (purified)	71.04
Carbomer viscosity control agents (commercially available in the Acritamer series from RITA corp.)	0.23
Alkyl Parabens	0.90
Glycerin	3.50
Potassium Hydroxide	0.09-0.15
Tetrasodium EDTA	0.10
Cetyl Alcohol	1.25
Stearic Acid	0.75
Glyceryl Stearate	0.63

Polyoxyethylene Stearyl Alcohol (sold under tradename BRIJ from ICI Americas, Inc.)	1.75
Coco-caprylate/caprate	2.00
C12-C15 Alcohol Benzoate (sold under tradename FINSOLV TN from Finetex, Inc.)	2.00
Di-(2-furyl) ethanedione dioxime (can be in anti-, syn-, amphi- form, or a combination thereof)	2.00
Octyl Methoxycinnamate	7.50
Benzophenone-3	1.00
Octyl Dimethyl PABA	1.00
Dimethicone	0.30
Imidazolidinyl Urea	0.10
Ethylene Acrylate Copolymer	3.80

Use of an amount of lotion sufficient to deposit about 0.04 mg/cm² of di-(2-furyl) ethanedione dioxime to the keratinous tissue is appropriate.

Example 2

A lotion suitable for use on skin, hair, nails, etc. is prepared by combining the following components utilizing conventional mixing techniques.

Component	Weight Percent
Water (purified)	55.64
Dimethyl Isosorbide	9.00
Dioctyl Maleate	8.00
C12-15 Alcohol Benzoate (FINSOLV TN - commercially available from Finetex, Inc.)	8.00
Glycerin	3.50
Ethylene Acrylate Copolymer	3.80
Di-(2-furyl) ethanedione monooxime (can be in syn- or anti- form or a combination thereof)	2.00
Tocopherol Sorbate	2.00
Cetyl Alcohol	1.75
Polyoxyethylene Stearyl Alcohol (commercially available in the BRIJ series from ICI Americas, Inc.)	1.75
Stearic Acid	1.25
Glyceryl Stearate	1.13
Alkyl Parabens	0.90
Titanium Dioxide	0.40
Dimethicone	0.30
Carbomer viscosity control agents (commercially available in the Acritamer series from RITA Corp.)	0.23
Imidazolidinyl Urea	0.10
Potassium Hydroxide	0.15
Tetrasodium EDTA	0.10

Use of an amount of lotion sufficient to deposit about 0.04 mg/cm² of di-(2-furyl) ethanedione monooxime to the keratinous tissue is appropriate.

Example 3

A cream suitable for use on skin, hair, nails, etc. is prepared by combining the following components utilizing conventional mixing techniques.

Component	Weight Percent
Tetrasodium EDTA	0.05
Alkyl Parabens	0.30
Carbopol (polyacrylic acid polymer - commercially available from B.F. Goodrich Chemical)	0.20
Glycerin	2.00
Laureth-23 (polyethylene glycol ether of lauryl alcohol)	3.00
Sorbitan Stearate	1.50
Octyl Dimethyl PABA	3.00
Dimethicone	2.00
Stearyl Alcohol	6.00
Triethanolamine	0.20
Di-(2-furyl) ethanedione monooxime (can be in syn- or anti- form or a combination thereof)	2.00
Water (purified)	q.s.

Use of an amount of cream sufficient to deposit about 0.04 mg/cm² of di-(2-furyl) ethanedione monooxime to the keratinous tissue is appropriate.

Example 4

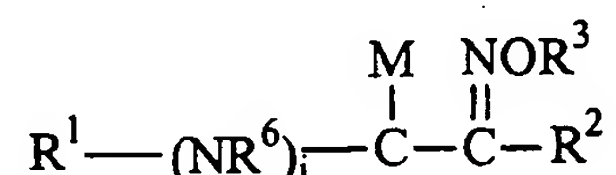
A gel suitable for use on skin, hair, nails, etc. is prepared by combining the following components utilizing conventional mixing techniques.

Component	Weight Percent
Ozokerite Wax	10.00
Paraffin	10.00
Petrolatum	10.00
Isopropyl Myristate	5.00
Mineral Oil	58.00
Propylparaben	0.10
BHA	0.05
1-phenyl-1,2-propanedione-2-oxime	2.00
Naproxen	2.00
Water (purified)	q.s.

Use of an amount of gel sufficient to deposit about 0.04 mg/cm² of 1-phenyl-1,2-propanedione-2-oxime to the keratinous tissue is appropriate.

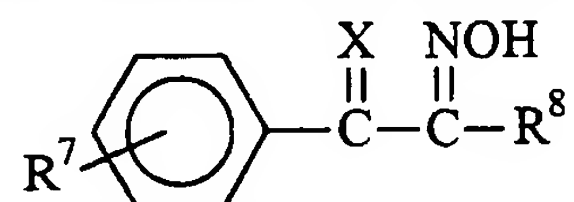
What is claimed is:

1. A method of lightening keratinous tissue wherein said method comprises the step of topically applying to the keratinous tissue in need of such treatment a safe and effective amount of a composition comprising a safe and effective amount of an oxime compound and a dermatologically acceptable carrier for the oxime compound.
2. The method of Claim 1 wherein said oxime compound has the structural formula:



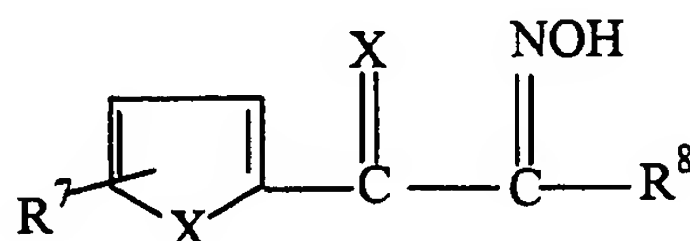
wherein $-R^1$ and $-R^2$ are independently selected from the group consisting of alkyl, aryl, and heteroaryl, wherein R^1 and R^2 may be covalently bonded together to form a cyclic alkyl; $-M$ is selected from the group consisting of $=O$, $=S$, $-SR^4$ and $-OR^4$ (when $-M$ is $-OR^4$ or $-SR^4$, there is a hydrogen bonded to the carbon to which $-M$ is bonded) and $-R^4$ is selected from the group consisting of hydrogen, alkyl, aryl, and heteroaryl; $-R^3$ is selected from the group consisting of hydrogen, alkyl, aryl and heteroaryl; and i is selected from the group consisting of one and zero.

3. The method of Claim 2 wherein said oxime compound is selected from the group consisting of di-(2-furyl) ethanedione syn-monooxime, di-(2-furyl) ethanedione anti-monooxime, and combinations thereof.
4. The method of Claim 1 wherein said oxime compound has the structural formula:



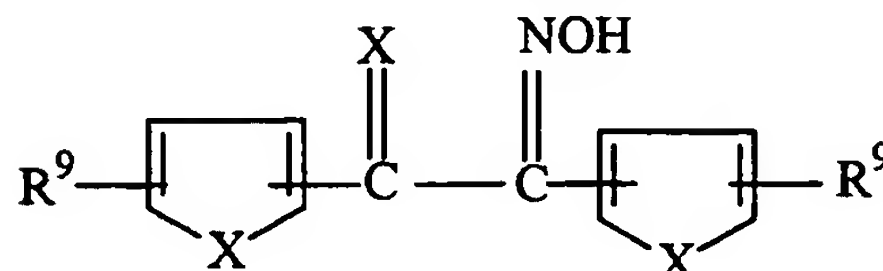
wherein $=X$ is $=O$ or $=S$, $-R^7$ is from 0 to 5 alkyl substituents, and $-R^8$ is C1-C8 alkyl.

5. The method of Claim 4 wherein said oxime compound is 1-phenyl-1,2-propanedione-2-oxime.
6. The method of Claim 1 wherein said oxime compound has the structural formula:



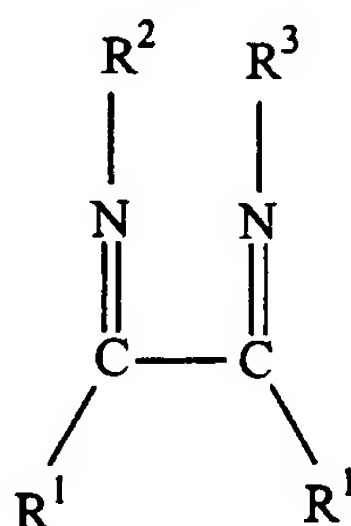
wherein each X is independently O or S , $-R^7$ is from 1 to 3 alkyl substituents, and $-R^8$ is C4-C8 alkyl.

7. The method of Claim 1 wherein said oxime compound has the structural formula:



wherein each X is independently O or S, no more than one $-R^9$ is hydrogen, and one or both $-R^9$ are independently from 1 to 3 alkyl substituents.

8. The method of Claim 1 wherein said oxime compound has the following structural formula:

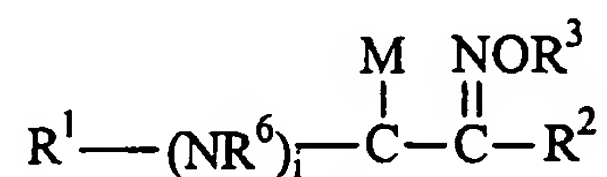


wherein each $-R^1$ is independently selected from the group consisting of alkyl, aryl, heteroaryl and heterocyclic, or the $-R^1$'s are covalently bonded together to form a cyclic alkyl ring; each heteroaryl, if any, being independently selected from the group consisting of furyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, pyrazinyl, isoquinolyl, purinyl, phthaliziny, quinoxaliny, furazanyl, isoxazolyl, and tetrazolyl; each heterocyclic ring, if any, being independently selected from the group consisting of the saturated analogs of the above listed group of heteroaryl rings;

wherein $-R^2$ and $-R^3$ are $-OR^4$ in which case there is no bond or polar bond between $-R^2$ and the nitrogen covalently bonded to $-R^3$, each $-R^4$ being independently selected from the group consisting of hydrogen, alkyl and aryl, except that both $-R^4$'s are not methyl when both $-R^1$'s are furyl; or $-R^2$ is $-O-$ and is covalently bonded to the nitrogen which is covalently bonded to $-R^3$, and $-R^3$ is $-O-$ there being a + charge on the nitrogen to which it is bonded or nil.

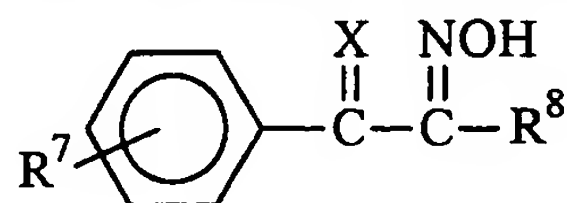
9. The method of Claim 8 wherein said oxime compound consists essentially of compounds wherein $=NR^2$ and $=NR^3$ are in amphi configuration when both $-R^2$ and $-R^3$ are $-OH$, and when both $-R^1$'s are furyl or the $-R^1$'s are covalently bonded together to form a cyclohexanedione structure.
10. The method of Claim 8 wherein said oxime compound is di-(2-furyl) ethanedione amphi-dioxime, di-(2-furyl) ethanedione anti-dioxime, di-(2-furyl) ethanedione syn-dioxime, and combinations thereof.

11. The method of Claim 1 wherein said composition comprises from about 0.001% to about 20%, by weight of the composition, of the oxime compound.
12. The method of Claim 1 wherein said composition comprises from about 0.01% to about 10%, by weight of the composition, of the oxime compound.
13. The method of Claim 1 wherein said composition comprises from about 0.1% to about 5%, by weight of the composition, of the oxime compound.
14. The method of Claim 1 wherein said composition comprises from about 0.5% to about 5%, by weight of the composition, of the oxime compound.
15. The method of Claim 1 wherein said composition further comprises additional actives selected from the group consisting of desquamatory actives, anti-acne actives, anti-wrinkle actives, anti-atrophy actives, anti-oxidants, radical scavengers, flavonoids, anti-inflammatory agents, anti-cellulite agents, topical anesthetics, tanning actives, additional skin lightening agents, antimicrobial agents, antifungal agents, additional chelating agents, sunscreen actives, conditioning agents, thickening agents, and combinations thereof.
16. A method of lightening keratinous tissue wherein said method comprises the step of topically applying to the keratinous tissue in need of such treatment a safe and effective amount of a composition comprising a safe and effective amount of an oxime compound selected from the group consisting of di-(2-furyl) ethanedione syn-monooxime, di-(2-furyl) ethanedione anti-monooxime, di-(2-furyl) ethanedione amphi-dioxime, di-(2-furyl) ethanedione anti-dioxime, di-(2-furyl) ethanedione syn-dioxime, 1-phenyl-1,2-propanedione-2-oxime, and combinations thereof and a dermatologically acceptable carrier for the oxime compound.
17. A method of lightening hyperpigmented regions of mammalian skin wherein said method comprises the step of topically applying to the skin in need of such treatment a safe and effective amount of a composition comprising a safe and effective amount of amount of an oxime compound and a dermatologically acceptable carrier for the oxime compound.
18. The method of Claim 17 wherein said oxime compound has the structural formula:



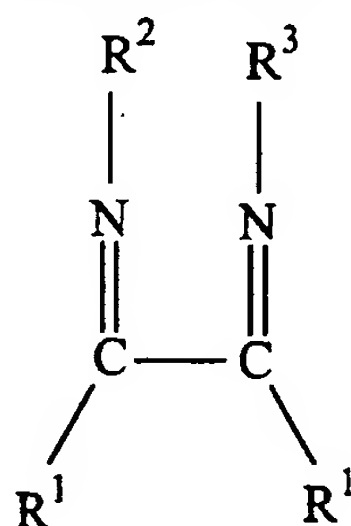
wherein $-R_1$ and $-R_2$ are independently selected from the group consisting of alkyl, aryl, and heteroaryl, wherein R_1 and R_2 may be covalently bonded together to form a cyclic alkyl; $-M$ is selected from the group consisting of $=O$, $=S$, $-SR_4$ and $-OR_4$ (when $-M$ is $-OR_4$ or $-SR_4$, there is a hydrogen bonded to the carbon to which $-M$ is bonded) and $-R_4$ is selected from the group consisting of hydrogen, alkyl, aryl, and heteroaryl; $-R_3$ is selected from the group consisting of hydrogen, alkyl, aryl and heteroaryl; and i is selected from the group consisting of one and zero.

19. The method of Claim 17 wherein said oxime compound has the structural formula:



wherein $=X$ is $=O$ or $=S$, $-R_7$ is from 0 to 5 alkyl substituents, and $-R_8$ is C1-C8 alkyl.

20. The method of Claim 17 wherein said oxime compound has the following structural formula:



wherein each $-R_1$ is independently selected from the group consisting of alkyl, aryl, heteroaryl and heterocyclic, or the $-R_1$'s are covalently bonded together to form a cyclic alkyl ring; each heteroaryl, if any, being independently selected from the group consisting of furyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, pyrazinyl, isoquinolyl, purinyl, phthaliziny, quinoxalinyl, furazanyl, isoxazolyl, and tetrazolyl; each heterocyclic ring, if any, being independently selected from the group consisting of the saturated analogs of the above listed group of heteroaryl rings;

wherein $-R_2$ and $-R_3$ are $-OR_4$ in which case there is no bond or polar bond between $-R_2$ and the nitrogen covalently bonded to $-R_3$, each $-R_4$ being independently selected from the group consisting of hydrogen, alkyl and aryl, except that both $-R_4$'s are not methyl when both $-R_1$'s are furyl; or $-R_2$ is $-O-$ and is covalently bonded to the nitrogen which is covalently bonded to $-R_3$, and $-R_3$ is $-O-$ there being a + charge on the nitrogen to which it is bonded or nil.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 00/18731

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K7/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication where appropriate, of the relevant passages	Relevant to claim No
E	WO 00 56702 A (COLLINGTON ERIC WILLIAM :GEDEN JOANNA VICTORIA (GB): PROCTER MARTI) 28 September 2000 (2000-09-28) page 10, line 5-19 page 34, line 19-27 page 36, line 16-18 examples 3-5,8,9,18,20,21,23 ---	1.2. 11-15. 17.18
E	EP 1 023 894 A (OREAL) 2 August 2000 (2000-08-02) claims 1,2 ---	1,11-15, 17
Y	WO 95 27485 A (PROCTER & GAMBLE) 19 October 1995 (1995-10-19) page 3, line 34 -page 4, line 4: examples V.X --- -/--	1-20

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

*** Special categories of cited documents:**

- *A* document defining the general state of the art which is not considered to be of particular relevance
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Date of the actual completion of the international search

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INTERNATIONAL SEARCH REPORT

Int. Application No.

PCT/US 00/18731

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	D. JANG: "Melanogenesis Inhibitor from Paper Mulberry" COSMETIC & TOILETRIES, vol. 112, 1997, page 59-62 XP000971365 page 60, paragraph 3 page 62, last paragraph	1-20
A	WO 91 16034 A (PROCTER & GAMBLE) 31 October 1991 (1991-10-31) the whole document	1-3, 11-18
A	WO 91 16035 A (PROCTER & GAMBLE) 31 October 1991 (1991-10-31) the whole document	1,8-17, 20

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No.

PCT/US 00/18731

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 0056702	A	28-09-2000	NONE	
EP 1023894	A	02-08-2000	FR 2788694 A CN 1267515 A JP 2000212033 A	28-07-2000 27-09-2000 02-08-2000
WO 9527485	A	19-10-1995	CA 2186867 A EP 0754039 A	19-10-1995 22-01-1997
WO 9116034	A	31-10-1991	AU 662101 B AU 7756591 A CA 2079485 A EP 0611301 A US 5364617 A	24-08-1995 11-11-1991 27-10-1991 24-08-1994 15-11-1994
WO 9116035	A	31-10-1991	AT 195247 T AU 656723 B AU 7747191 A CA 2079486 A DE 69132363 D EP 0596876 A ES 2148149 T US 5462963 A	15-08-2000 16-02-1995 11-11-1991 27-10-1991 14-09-2000 18-05-1994 16-10-2000 31-10-1995